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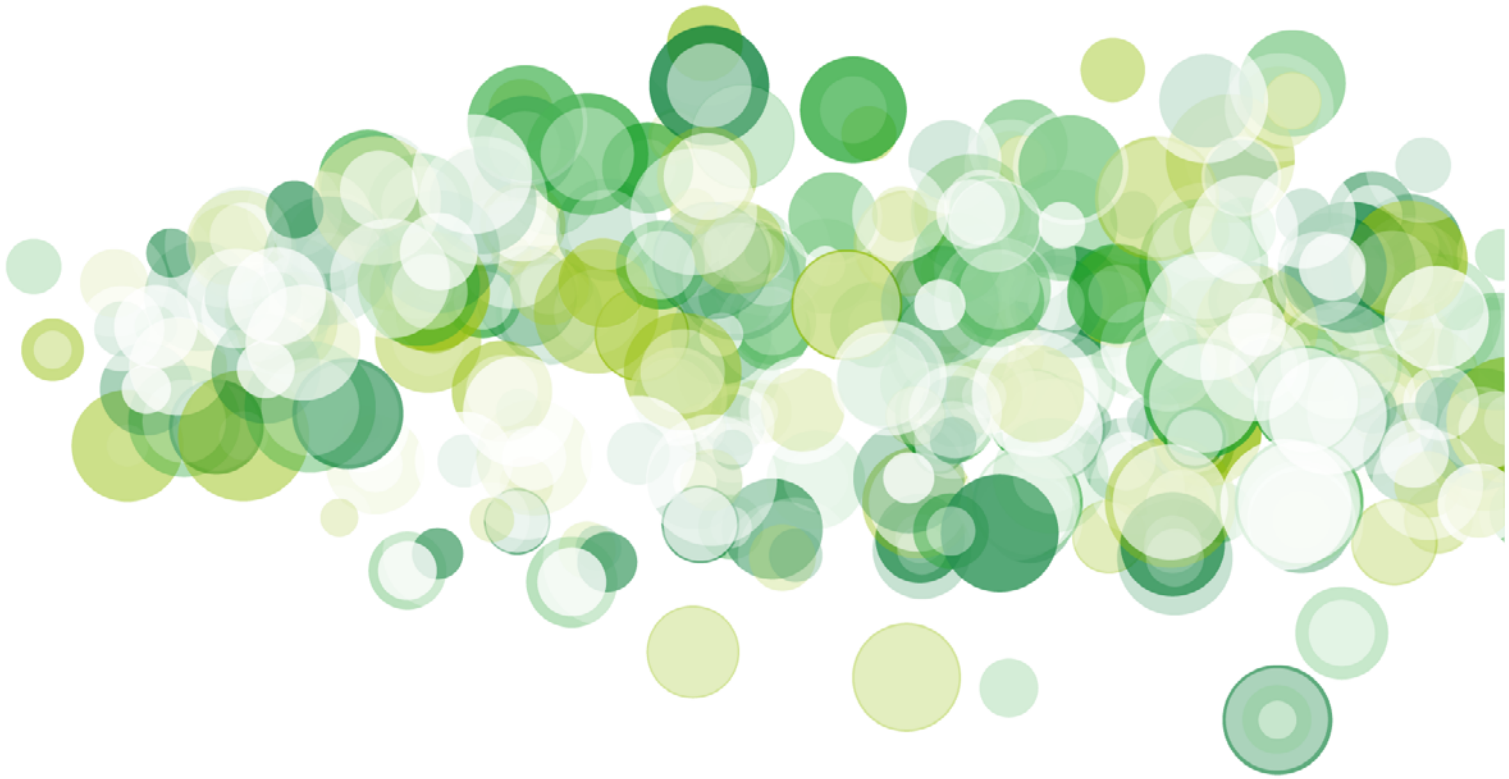

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EDITORIAL

Welcome

Bienvenida

Cristina Duboscq (CLAHT) and Joan C. Reverter (SETH)*

Editors-in-Chief

Dear Colleagues,

We are honored to present the first issue of the new *Hemostasia y Trombosis – Revista Iberoamericana de Trombosis y Hemostasia,* now the official journal of the Spanish Society of Hemostasis and Thrombosis (SETH) and the Latin American Group of Hemostasis and Thrombosis (CLAHT Group). This new publication inherits the spirit of the former *Revista Iberoamericana Journal de Trombosis y Hemostasia,* which was published from 1988 through 2002. It has now been updated and sights have been set in the future.

This journal is launched with the ambition of becoming the go-to space for scientific exchange among the community of researchers and clinicians specializing in this field of medicine and biology. We aspire to create a space where new ideas and findings become tools that drive the development and enhancement of clinical practice in thrombosis and hemostasis.

Our objective is to promote the dissemination of knowledge, constructive debate, and continuous updates through the publication of various types of articles on any aspect related to hemostasis and thrombosis, such as original studies, reviews, case reports, letters to the editor, clinical practice guidelines, editorials, and images.

Hemostasia y Trombosis – Revista Iberoamericana de Trombosis y Hemostasia is a quarterly, open-access, free publication for authors and readers, peer-reviewed, published in bilingual electronic format, and accepts manuscripts for evaluation in both Spanish and English. The journal has an editorial board of experts across the various aspects of hemostasis and thrombosis. Open access guarantees maximum visibility for all published works, and peer review ensures their quality and scientific rigor. The absence of a cost for authors allows for full accessibility for potential contributors. Publishing in both Spanish and English aims to encourage participation from diverse readership and authorship profiles.

We aspire to create a space where new ideas and discoveries become tools that drive the development and refinement of clinical practice in the field of thrombosis and hemostasis.

We encourage you to make this journal your own by contributing your findings and reflections (https://www.revistahemostasiaytrombosis.com/). We are confident that, through this editorial space, we can explore the challenges and horizons of our discipline, where hemostasis and thrombosis are addressed with the precision that patients deserve.

We eagerly await your contributions, with optimism and trust that through shared efforts, we will help to build knowledge in this exciting field.

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Hemostasia y Trombosis
REVISTA IBEROAMERICANA DE TROMBOSIS Y HEMOSTASIA

Editorial

Editorial

Cristina Duboscq (CLAHT) and Joan C. Reverter (SETH)*
Editors-in-Chief

Although interest in blood coagulation processes has accompanied humanity since ancient times, the mechanisms and clinical management of coagulation-related issues have historically been poorly understood. In recent decades, hemostasis and thrombosis have seen spectacular advancements that have transformed clinical practice. This issue of the journal includes contributions in several areas relevant to our field, specifically bleeding disorders, thrombosis, coagulation laboratory techniques, and the application of artificial intelligence to hemostasis.

Bleeding disorders: an unresolved challenge

From hemophilia A and B and other plasma coagulation defects to hereditary or acquired platelet disorders, bleeding disorders pose a significant diagnostic and therapeutic challenge. Recent years have seen a revolution in the treatment of these entities, including improvements in coagulation factor replacement therapy with extended-action agents, the introduction of bispecific antibodies, the development of rebalance therapies, and the emergence of gene therapy. This range of options brings us closer to the possibility of individualizing treatments for optimal patient management.

Similarly, in the management of thrombocytopathies, the development of advanced testing for platelet function has improved our diagnostic capacity, although treatment remains limited, often focused only on nonspecific hemostatic agents. Basic and translational research is crucial for better therapeutic options.

This issue includes two collaborative articles on bleeding disorders, one on mild hemophilia A and B and another on immune thrombocytopenia treatment. Collaboration within cooperative groups is essential, especially in the management of rare diseases.

Thrombosis and antithrombotic treatment: an era of progress and hope

Although there have been remarkable advances in thrombosis and antithrombotic treatment, much work remains. The introduction of vitamin K antagonists in the mid-20th century marked a paradigm shift in thrombosis prevention, providing an effective means for controlling thromboembolic risk. The development of direct oral anticoagulants heralded a new era characterized by greater safety, ease of use, and reduced monitoring needs, revolutionizing the management of thromboembolic disease. Although significant progress has been made in antiplatelet therapy, there remains ample room for improvement in all aspects of antithrombotic treatment, including drugs and health care organization. Currently, new lines of anticoagulant drugs are in the pipeline, with the most promising being the inhibitors of the intrinsic coagulation pathway. Additionally, the multidisciplinary model of specific antithrombotic treatment units is being discussed and defined, with accreditation as a step toward excellence.

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From a thrombosis biology perspective, we are in a phase of expanding knowledge, highlighting the relationship between thrombosis and the immune system and inflammation, from the well-known antiphospholipid syndrome to immunothrombosis phenomena and anti-platelet factor 4 syndromes.

This issue presents a case report of an antiphospholipid syndrome progressing from silent to catastrophic antiphospholipid syndrome, challenging the notion of "innocent" antiphospholipid antibodies in some patients.

The hemostasis lab: toward an era of diagnostic precision

The hemostasis laboratory is a cornerstone in diagnosing and monitoring thrombotic and bleeding disorders. From the classic prothrombin time and activated partial thromboplastin time tests to more modern thrombin generation assays and platelet function analyses, we have come a long way in characterizing coagulation disorders.

Currently, new technologies and methodologies such as proteomics and next-generation sequencing are revolutionizing the lab diagnostic capabilities with increasing precision.

The true challenge lies in integrating these data into everyday clinical practice. Integrated diagnostic models combining conventional laboratory parameters with emerging biomarkers and artificial intelligence-based algorithms have the potential of transforming how we diagnose and treat thrombotic and bleeding disorders. A.I. not only facilitates handling large datasets but also enables the identification of hidden correlations among diverse clinical factors, suggesting more effective therapeutic strategies.

This issue presents an original study evaluating a paired testing strategy for lupus anticoagulant diagnosis, which was found to be technically useful and economically favorable.

Looking ahead: new tools and an comprehensive vision

One of the main challenges is managing thrombotic and bleeding risk in increasingly complex patients. The identification of biomarkers and the genetic profile associated with characteristics of each individual is driving intense research with the goal of providing increasingly personalized prophylaxis and treatments toward precision medicine.

The rise of A.I. brings a new tool for analyzing complex data. Its ability to process large volumes of data in real-time by integrating genetic, proteomic, functional, and other information may potentially redefine diagnostic and predictive precision, allowing for quicker, more detailed identification of analytical patterns and drug response. In this way, we expect predictive models that optimize patient diagnosis and treatment to be more readily developed.

This issue includes an article evaluating the application of A.I. for comparing results from two treatments for immune thrombocytopenia.

Hemostasia y Trombosis
REVISTA IBEROAMERICANA DE TROMBOSIS Y HEMOSTASIA

ORIGINAL ARTICLE

Galician-Asturian experience of avatrombopag use in immune thrombocytopenia

Experiencia galaico-asturiana de uso del avatrombopag en la trombocitopenia inmunitaria

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Abstract

Introduction: *Avatrombopag, a second-generation thrombopoietin receptor agonist (TPO-RA), has been approved to treat chronic immune thrombocytopenia (ITP) in adults and in patients with chronic liver disease before surgery. Introduced in the pharmacotherapeutic guide of hospitals in Galicia and Asturias (Spain) in 2023, this medication offers an option for patients who do not adequately respond to other treatments.* **Objective and method:** *This retrospective observational study evalua tes the efficacy of avatrombopag in 55 patients with ITP, focusing on those treated in hospitals in Galicia and Asturias over 18 months. Of these, 53 had persistent/chronic ITP, and the majority were middle-aged women with a mean age of 64.7 years. Most patients (85.45%) had primary ITP and used avatrombopag as second or third-line treatment.* **Results:** *94.45% of patients achieved a sustained response with a platelet count greater than 30 × 10^9/L. Additionally, a rapid response to avatrombopag was observed, with a median time to response of only 7 days. Despite some cases of serious adverse effects such as suspected medullary fibrosis and thromboembolism, overall tolerance to the medication was good.* **Conclusions:** *The study highlights the importance of customizing treatment according to individual patient characteristics and considering factors such as age and comorbidity. With an individualized approach, avatrombopag emerges as an effective and safe option for managing chronic ITP, offering a promising alternative to conventional therapies.*

Keywords: *Immune thrombocytopenia. TPO-RA agonists. Efficacy. Safety. Thrombosis.*

Resumen

Introducción: *El avatrombopag, un agonista del receptor de trombopoyetina (TPO-RA) de segunda generación, ha sido aprobado para tratar la trombocitopenia inmunitaria o púrpura trombocitopénica inmunitaria (PTI) crónica en adultos y en pacientes con enfermedad hepática crónica antes de una cirugía. Introducido en la guía farmacoterapéutica de los hospitales de Galicia y Asturias en 2023, este fármaco ofrece una opción para pacientes que no responden adecuadamente a otros tratamientos.* **Objetivo y método:** *Este estudio observacional retrospectivo evalúa la eficacia del avatrombopag en 55 pacientes con PTI, enfocándose en aquellos tratados en hospitales de Galicia y Asturias durante 18 meses. De estos, 53 tenían PTI*

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persistente o crónica, y la mayoría eran mujeres con una edad media de 64.7 años. La mayoría de los pacientes (85.45%) presentaban PTI primaria y utilizaban avatrombopag como segunda o tercera línea de tratamiento. **Resultados:** *El 94.45% de los pacientes alcanzaron una respuesta sostenida, con un recuento de plaquetas superior a 30 × 10^9/l. Además, se observó una rápida respuesta al avatrombopag, con una mediana de tiempo hasta la respuesta de solo 7 días. A pesar de algunos casos de efectos adversos graves, como sospecha de fibrosis medular y tromboembolia, la tolerabilidad general fue buena.* **Conclusiones:** *El estudio destaca la importancia de personalizar el tratamiento según las características individuales de cada paciente y considerar factores como la edad y la comorbilidad. Con un enfoque individualizado, el avatrombopag se presenta como una opción efectiva y segura para el manejo de la PTI crónica, ofreciendo una alternativa prometedora a las terapias convencionales.*

Palabras clave: *Trombocitopenia inmunitaria. Agonistas de TPO-RA. Eficacia. Seguridad. Trombosis.*

Introduction

Avatrombopag, a second-generation oral thrombopoietin receptor agonist (TPO-RA), has been approved for the treatment of chronic immune thrombocytopenia or immune thrombocytopenia purpura (ITP) in adults who are refractory or have an inadequate response to other treatments. It is the first TPO-RA approved for adults with chronic liver disease scheduled for surgery[1]. In Galicia and Asturias, Spain it was included in the 2023 hospital pharmacotherapeutic guidelines.

The prevalence of ITP is 9.5 cases per 100,000 adults, with an incidence of 3.3/100,000 adults per year, increasing with age[2], with no gender differences except between the ages of 30 and 60, when it is more prevalent in women[3], and in individuals older 70, when it predominantly affects men. Mortality is higher in older ages, and its prevalence is 3 times higher vs younger adults. In adults, primary ITP accounts for 80% of cases, with the remaining 20% being due to other conditions.

In older adults, compared to children and young adults, it tends to be more chronic, with less likelihood of spontaneous remissions and a risk of progressing to other conditions. There is a higher incidence of hematological malignancies, such as lymphomas and leukemias (increased risk by 6 and 20 times, respectively)[4], and a higher predisposition to autoimmune diseases.

In chronic liver disease[5], platelet transfusions[6] are the choice for non-elective surgical procedures, especially major ones, and for elective procedures when TPO-RAs are unavailable or inadequate[7]. These transfusions carry various risks. The Subcommittees for Standardization of the International Society on Thrombosis and Hemostasis[7] state that TPO-RAs can be offered to patients with platelet counts of 30-50 × 10^9/L without risk factors for venous thromboembolism (VTE) undergoing high-bleeding risk elective surgery.

This study reports the experience of switching to avatrombopag and its use as a first-line therapy in second-line therapy for adults with chronic ITP in hospitals in Galicia and Asturias, Spain over 18 months. Additionally, 2 patients with newly diagnosed ITP on avatrombopag as first-line therapy (6-month follow-up) are included.

Method

We conducted a retrospective observational study; data were obtained from the patients' electronic health records, with informed consent. Data are expressed as percentages, medians, interquartile ranges (IQR), and means with standard deviation (SD), as appropriate. Patients on avatrombopag as first-line therapy are analyzed separately.

Results

A total of 55 patients were included, 53 of whom had persistent or chronic ITP. Forty-five (85%) had chronic ITP, with a mean age of 64.7 years (SD, 20.32). A total of 66% of the patients were women, 85.45% (45/55) had primary ITP. A total of 43.4% our of all the chronic ITP patients, received avatrombopag as second-line therapy, and the rest (56.6%) as third-line therapy or sometime later (median, 3; IQR, 2-12). A total of 27 patients had previously received a TPO-RA, and 26 had not. The median follow-up was 163.5 days (IQR, 97.5-233.5). In 47 (88.67%) patients, the mean starting dose was 140 mg per week. One patient had received 12 prior lines of treatment.

A total of 94.45% of patients achieved a sustained response (> 30 × 10^9/L), and 90.57% a platelet count > 50 × 10^9/L. The median time to response (platelets > 30 × 10^9/L) was 7 days (IQR, 7-11). Eight patients (18.2%) who started on avatrombopag as second-line therapy or sometime later discontinued it due to no

response, adverse effects (suspected bone marrow fibrosis, thrombocytosis, and intolerance), and 1 death unrelated to the drug. Overall tolerability was good, with 1 case of grade 2 bone marrow fibrosis and 1 pulmonary embolism in a patient with a positive lupus anticoagulant. The patient with bone marrow fibrosis was later diagnosed with Tangier syndrome instead of ITP.

At the last visit, the median platelet count was 120.5 × 10^9/L (IQR, 16-468 × 10^9/L), with highly variable weekly doses: up to 15 different dosing regimens in 46 patients (mean, 149.13 mg per week; SD, 20-280) (Table 1).

By gender (n = 53), 18 patients were men (33.96%), 6 of whom (30%) were younger than 65, and 7 (38.88%) received avatrombopag as third-line therapy or sometime later; 4 out of these 7 had previously received eltrombopag and 3, romiplostim. Another 11 (61.12%) were on avatrombopag as second-line therapy. There was no discontinuation of avatrombopag in this group. The median dose (n = 18) was 140 mg (IQR, 20-280), with dose titration in 13/18 patients (72.2%). The mean weekly dose of avatrombopag after switching from a previous agonist was similar regardless of the drug: from eltrombopag (n = 3), the mean weekly dose was 166.6 mg, and from romiplostim (n = 4), 160 mg. In the remaining men (n = 12), the mean weekly dose was lower (134.54 mg). Four of the 18 patients required the maximum weekly dose of avatrombopag (280 mg) to maintain platelet counts. Overall, in men, the median platelet count at the last check was 143 × 10^9/L (IQR, 16-272 × 10^9/L) (Tables 2 and 3).

Thirty-five out of the 53 patients were women (66.04%), and 19 (54.28%) were younger than 65. Twenty (57.1%) were on avatrombopag as a third-line therapy or sometime later: 14 had previously received eltrombopag, and 6, romiplostim. Six (17.14%) were on avatrombopag as a second-line therapy, and 9 (25.7%) had received other previous treatments. Seven discontinuations were reported: 5 in previous agonist recipients and 2 in third-line therapies or later avatrombopag recipients without a previous agonist.

The median avatrombopag dose (n = 28) was 140 mg (IQR, 60-280); dose titration was required in 19/28 (67.8%). The mean weekly dose of avatrombopag in responders from eltrombopag (n = 10) was 184.1 mg, from romiplostim (n = 5) it was 148.1 mg, and in the rest (n = 13) it was slightly lower (115.38 mg). Six patients required the maximum weekly dose of avatrombopag to maintain platelet counts. At the last check, the median platelet count was 112 × 10^9/L (IQR, 36-468). The mean platelet count in patients with previous eltrombopag was 98.7 × 10^9/L (SD, 62-204 × 10^9/L), with previous romiplostim it was 152.2 × 10^9/L (SD, 39-275), and without previous agonists it was 144.8 × 10^9/L (SD, 36-468 × 10^9/L). Notably, previous eltrombopag recipients had, on average, 4 prior lines of therapy before avatrombopag (SD, 3-7), with no response in those with more than 7 lines of therapy vs the previous romiplostim group (mean, 2.25; SD, 1-4). Better responses were obtained with lower avatrombopag doses in patients without prior a agonist, regardless of gender (Tables 2 and 3).

By age groups, 13/28 patients older than 65 switched from a previous agonist (7 from romiplostim and 6 from eltrombopag), with 10 maintaining the response after the switch, while 15 responded to avatrombopag as a second-line therapy. Three patients discontinued treatment (due to intolerance, suspected myelofibrosis, and death). Dose titration was required in 21/25 patients

Table 1. General characteristics of the studied population

Characteristics	Description
Total patients (n)	55
Patients with de novo ITP (n)	2
Patients with chronic ITP (n)	45 (85%)
Mean age (years)	64.7
Gender distribution (%)	Female: 66 Male: 34
Primary ITP (n)	45 (85.45%)
Avatrombopag as second-line therapy	43.4%
Avatrombopag as third-line or beyond	56.6%
Median follow-up	163.5 days
Mean initial dose of avatrombopag	140 mg (88.67% of patients)
Patients achieving partial response (platelets ≥ 30 × 10^9/L)	94.45%
Patients achieving complete response (platelets ≥ 50 × 10^9/L)	90.57%
Patients achieving platelet count ≥ 100 × 10^9/L	81.13%
Median time to response (platelets ≥ 30 × 10^9/L)	7 days
Patients discontinuing avatrombopag as second-line theraoy or beyond (n)	8 (18.2%); 6/8 women (75%)
Median platelet count at last visit	120.5 × 10^9/L

Table 2. Results by gender (n = 53)

Characteristics	Men	Women
Total number	18 (33.96%)	35 (66.04%)
Under 65 years	30%	54.28%
Avatrombopag as third-line therapy or beyond	7 (38.8%)	20 (57.1%)
Median weekly dose of avatrombopag	140 mg	140 mg
Patients requiring dose titration	13 (72.2%)	19 (67.8%)
Patients requiring maximum weekly dose	4	6
Median platelet count at last visit	143 × 10^9/L	112 × 10^9/L

Table 3. Results by gender and previous treatment (n = 27)

Characteristics	Men	Women
Total number	(7/18, 33.96%)	(20/35, 66.04%)
After romiplostim	3/7	6/20
Responders/Patients needing maximum dose	3/1	5/1
Mean weekly dose of avatrombopag	160 mg	148.1 mg
Mean platelet count	183.2 × 10^9/L	152.2 × 10^9/L
Patients needing maximum weekly dose	1	1
After eltrombopag	4/7	14/20
Responders/patients needing maximum dose	4/1	10/5
Mean weekly dose of avatrombopag	166.6 mg	184.1 mg
Median platelet count at last visit	106 × 10^9/L	98.7 × 10^9/L

(84%), and 6/25 (24%) required the maximum weekly dose to maintain platelet counts ≥ 50 × 10^9/L. The median last platelet count was 137 × 10^9/L (IQR, 16-334 × 10^9/L), with a median weekly dose of avatrombopag of 140 mg (IQR, 40-280 × 10^9/L).

There are 25 patients younger than 65, 14 of whom (56%) started on avatrombopag after another previous agonist (11 on eltrombopag and 3 on romiplostim). Of these, 11 maintained the platelet response after the switch, and 3 from the eltrombopag group discontinued treatment (thrombocytosis, 2 due to relapse or lack of response). Ten of the 11 patients on avatrombopag as

Table 4. Results by age (n = 53)

Characteristics	< 65 years	≥ 65 years
Total number	25 (47.16%)	28 (52.83%)
Patients from another TPO-RA	14/25 (56%)	13/28 (46.42%)
Patients responding after previous agonist	11/14 (78.57%)	10/13 (76.92%)
Patients responding to avatrombopag as second-line therpy	10/11 (90.9%)	15/15 (100%)
Median weekly dose of avatrombopag	140 mg	140 mg
Patients requiring dose adjustment	19/25 (76%)	21/25 (84%)
Patients requiring maximum weekly dose (280 mg)	4 (16%)	6/25 (24%)
Median platelet count at last visit	112 × 10^9/L	137 × 10^9/L

the first-line agonist in second-line therapy achieved a response, with 1 discontinuing treatment due to loss of response. The median last platelet count (n = 21) was 112 × 10^9/L (IQR, 36-468 × 10^9/L), lower than in the older group, with a median weekly dose of 140 mg (IQR, 20-280), which is similar to the older-than-65 group. A total of 19 out of the 25 patients (76%) required dose titration. Four patients maintaining platelet response with the maximum weekly dose switched from eltrombopag (Table 4).

By previous lines of therapy, 26 received avatrombopag as a second-line therapy, 57.69% of whom were women. Of these 26 patients, 12 (46.15%) required dose titration, and only 2 required the maximum weekly dose to maintain platelet counts. The median last platelet count was 138.5 × 10^9/L (IQR, 29-468 × 10^9/L), with a median weekly dose of avatrombopag of 130 mg (IQR, 20-280) (n = 24). Two patients discontinued treatment (due to loss of response and death).

Of the 53 patients, 27 received 3 or more previous lines of therapy, 19 of whom (70.37%) were women. Of these 27 patients, 5 discontinued therapy (due to intolerance, relapse, lack of response, suspected bone marrow fibrosis, and thrombocytosis). Dose titration was required in 20/23 patients, and 8/23 patients maintained the response with the maximum weekly dose of avatrombopag. The median platelet count (n = 23) was 104 × 10^9/L (IQR, 16-275 × 10^9/L), with a median weekly

Table 5. Results by therapy line (n = 53)

Characteristics	Second-line therapy	Third-line therapy or beyond
Total number	26	27
Female patients	57.69%	70.37%
Median weekly dose of avatrombopag	130 mg	155 mg
Patients responding	24/26 (92.3%)	23/27 (85.18%)
Patients requiring dose adjustment	12/26 (46.15%)	20/23 (86.95%)
Patients requiring maximum weekly dose (280 mg)	2/24 (8.33%)	8/23 (34.78%)
Median platelet count at last visit	138.5 × 10^9/L	104 × 10^9/L

dose of 155 mg (IQR, 60-280). Seventeen out of 27 patients had previously received eltrombopag, with 13/17 maintaining the response after the switch (4 discontinued due to thrombocytosis, suspected myelofibrosis, relapse, and lack of response). The mean platelet count (n = 13) was 100.3 × 10^9/L (SD, 62-204 × 10^9/L), with a mean weekly dose of 193.84 mg (SD, 100-280). Up titration was required in 12/13 patients, with 6 maintaining the response with the maximum weekly dose of avatrombopag (mean platelet count: 96.8 × 10^9/L; SD, 71-108 × 10^9/L). Ten out of 17 patients switched from romiplostim, with 9 maintaining the response with a mean weekly dose of 151.11 mg (SD, 60-280); 1 discontinued due to intolerance. The mean platelet count was 166 × 10^9/L (SD, 16-275 × 10^9/L). Nine patients required dose titration, and 2 maintained the response with the maximum weekly dose (Table 5).

Two patients (7.7%) had newly diagnosed ITP (< 3 months), with a mean age of 81.5 years (range, 66-97), both women. The mean platelet count before starting avatrombopag was 16.5 × 10^9/L, and they had comorbidities, some associated with increased bleeding risk (female gender, hypertension, diabetes mellitus). The initial avatrombopag dose was 280 mg per week in both cases, with subsequent dose adjustment in one. The mean time to response was 7 days (mean platelet count: 136 × 10^9/L; range, 52-220 × 10^9/L). At the 6-month follow-up, they maintained a mean platelet count of 104 × 10^9/L (range, 51-157 × 10^9/L) with a mean weekly dose of avatrombopag of 170 mg (range, 60-280). Tolerability was good; one case of headache with the maximum dose resolved with dose reduction.

Discussion

The goal of ITP treatment is to achieve a safe platelet count to prevent or stop bleeding (> 20-30 × 10^9/L), at least, in symptomatic patients. Consideration should be given to lifestyle, age, comorbidities, and patient expectations, and therapeutic goals should be individualized according to the patient's disease phase[4,7,8]. Treatment-related aspects should also be considered, avoiding unnecessary drugs and being alert to toxicities and side effects. First-line therapy is corticosteroids[4,7,8], highly effective but no stranger to side effects. As second-line therapy, the Spanish ITP Group recommends TPO-RAs, including avatrombopag, although fostamatinib is suggested as an option for patients with high thrombotic risk[7].

Age can influence the efficacy and treatment-related toxicities. It is important to provide care that allows patients to reintegrate into their daily lives as quickly as possible, with safe platelet counts and minimal iatrogenesis[7,8]. Although corticosteroids are the treatment of choice, other first-line options, such as TPO-RAs[9], are being explored, which due to their safety and efficacy profile, even considering their slightly higher thrombotic risk could be the second-line option in patients unresponsive to first-line therapy, or even be first-line options when corticosteroids are contraindicated or expected to have undesirable side effects. This first-line use is not approved outside the clinical trial setting[7]. In our registry, patient age and gender do not seem to influence the response to avatrombopag.

In a controlled strial[10], patients with chronic ITP (≥ 12 months) and low baseline platelet counts (mean of 2 platelet counts < 30 × 10^9/L) were randomized to a 6-month regimen of placebo (n = 17) or avatrombopag (n = 32). The initial dose was 20 mg/day, titrated to minimum and maximum doses of 5 and 40 mg/day based on response (n = 32). After 26 weeks, those not participating in the subsequent open-label extension phase entered a down titration phase (4 weeks), with another 4 weeks of follow-up. Concomitant use of other standard treatments for chronic ITP and bailout therapy was allowed. A total of 47% of avatrombopag recipients and 41% of placebo recipients received concomitant medication for ITP at the beginning of the study, while 34% and 29%, respectively, were splenectomized. Avatrombopag showed rapid response and sustained efficacy: 65.6% had platelet counts ≥ 50 × 10^9/L by day 8, compared to 0% from the placebo group. Additionally, they maintained platelet counts ≥ 50 × 10^9/L longer without bailout therapy (median: 12.4 vs. 0 weeks in the placebo group). The median platelet count after the visit day was higher in the avatrombopag group (80.5 × 10^9/L

vs 8 × 10^9/L in the placebo group) from day 8 onwards. Efficacy was maintained in an extension phase of this trial. After completing the placebo-controlled phase, patients could continue avatrombopag treatment (maximum exposure duration in both phases: 76 weeks)[11]. In our registry, the median time to response, defined as a platelet count ≥ 30 × 10^9/L, was 7 days.

In a post hoc analysis during the extension phase, the adverse event profile was similar to that reported with other TPO-RAs. The efficacy of avatrombopag was studied in a trial comparing it with eltrombopag, but it was stopped early without conclusions[12]. The authors emphasize the rapid response to avatrombopag vs other agonists, which is important when choosing treatment[10]. In our registry, chronic ITP shows this rapid response (median of 7 days), though limited by the small sample size (n = 53) and short follow-up time (median of 165 days), but in line with the findings reported by other groups. The AVAMAD[13] trial reports the experience of switching to avatrombopag in 10 centers in Madrid, with 66 patients, from July 2022 through May 2023. Patients are similar to those from our series: median age 52 years (IQR, 34-71), 55% younger than 65 (vs. 43.39%) and 53% women (vs. 66%). At avatrombopag initiation, 73% had chronic ITP, and 83% primary, with a median platelet count of 36 × 10^9/L. A total of 88% started with 20 mg/day, and > 70% needed dose titration. Regarding previous treatment lines before the switch, 40% received avatrombopag as second-line therapy, 23% as third-line therapy, and 36% as a different line of therapy. One patient received avatrombopag as first-line therapy. A total of 70% of patients switched due to loss of response to previous treatment or refractoriness or corticosteroid dependence (60% had previous corticosteroids). The median follow-up was 212 days, with 86% responses, 73% complete (platelets > 100 × 10^9/L); in our registry, responses were 90.57% and 81.13%, respectively. More complete responses are seen with fewer prior therapy lines (1 vs. 3.5; p < 0.001). The median time to response was 2.1 weeks. The drug was safe; the most common side effect (15%) was headache. A total of 6 out of 66 patients had no response and discontinued treatment (in our registry, 8 of 53 patients). The switch experience reported by Al-Samkari et al.[14] shows similar results in 44 patients. The main reason for switching was convenience (52%), while 32% switched due to previous treatment inefficacy. The switch effectively rescued patients with previous agonist failure (93% platelet response [> 50 × 10^9/L] and 86% complete [> 100 × 10^9/L]), reducing the need for concomitant treatment (63% stopped corticosteroids after switching). In our initial results[15], we reported that 37.5% of patients were in previous response with another TPO-RA and maintained it after the switch, sometimes reducing the need for treatment to maintain the same platelet count; data pending confirmation. In this update, 81.13% of patients achieve and maintain platelet counts > 100 × 10^9/L, which is similar to AVAMAD data (73%), with higher response rates when used as second-line therapy, regardless of age and gender, influenced by the number of previous therapy lines. In second-line therapy, although the rate of response is similar (92.3% vs 85.18%), lower doses are needed (20% less), fewer dose titrations (50% less), and fewer patients require the maximum weekly dose of avatrombopag to maintain a platelet count ≥ 50 × 10^9/L.

As first-line therapy, an American group[16] hypothesized that avatrombopag is safe and effective at any disease phase. In an observational, multicenter cohort trial of adults with ITP on avatrombopag, the outcomes of 75 patients were compared: 23 with newly diagnosed or persistent ITP and 52 with chronic ITP. With avatrombopag, 91% of patients with newly diagnosed or persistent ITP, vs. 96% of chronic patients, achieved a platelet response (≥ 50 × 10^9/L/mL), and 86%, vs. 81% (p = 0.78), had a complete response (≥ 100 × 10^9/L), with a similar median platelet count (165 × 10^9/L vs 129 × 10^9/L; p = 0.57). Long response duration was reported, similar in both groups, without severe bleeding, VTE, or avatrombopag discontinuation. No other drug-related adverse events were reported. In our case, 2 patients received avatrombopag as first-line therapy and achieved a platelet response (> 50 × 10^9/L) quickly (mean, 7 days); only 1 patint achieved a complete response (> 100 × 10^9/L). The AVAMAD[13] trial included 1 patient on avatrombopag as first-line therapy, but we have no follow-up data, and our small sample size prevents drawing conclusions or comparisons with Virk et al.[16].

When patients can choose any of the 3 available TPO-RAs, our practice, in line with the literature[7], is to let them decide after presenting the options with their pros and cons. One reason for switching to avatrombopag is convenience or patient preference; in the AVAMAD trial, this accounted for 8%, and in our initial registry data[15], it accounted 37.5% of the changes, due to oral administration, no food interferences, and no need to respect fasting periods.

The thrombotic risk of TPO-RAs is also associated with corticosteroid and immunoglobulin use[17]. In our registry, 1 case of VTE (1 patient with risk factors) was treated initially with low molecular weight heparin and later with vitamin K antagonists, maintaining avatrombopag. Various reports indicate an increased thrombotic risk in

ITP patients[18]. The estimated VTE risk increase is, at least, 2-fold, particularly high within the first year after diagnosis, comparable to other autoimmune diseases and regardless of platelet count[2]. Additionally, althoughit occurs even with platelet counts < 30 × 10^9/L, the reasons for this increased risk in ITP remain unclear. Factors include increased circulating procoagulant microparticles, a proinflammatory state, the presence of immature and apoptotic platelets, a high prevalence of clinical thrombotic predisposition factors, antifospholipid antibodies, or increased neutrophil extracellular traps[19,20]. Additional risk factors include side effects of therapies such as TPO-RAs, which seem to increase the risk of vascular episodes, although less so when administered for non-ITP indications[21] and generally in patients who, like ours, are susceptible to these disorders due to age (> 60 years) or conditions such as hypertension, diabetes mellitus, or overweight[8]. Regarding VTE risk, TPO-RAs seem to increase it 2- to 3-fold, with no differences between them, being the risk higher within the first year after therapy initiation[3]. Compared directly with placebo, no agonist increased the VTE rate[21], and the risk is also recognized to increase in untreated ITP patients. Some authors[22] and guidelines[7] recommend fostamatinib as first choice in second-line therapy for patients with high thrombotic risk; in our opinion, this is debatable because RIETE[23] reported risk factors are the same as in ITP and are compounded by the ITP *per se*[24]. In a Spanish consensus on ITP treatment, panelists disagreed on this option[25]. A possible strategy suggested by Ghanima et al.[26] is to consider anticoagulation or antiplatelet therapy when the platelet count is ≥ 50 × 10^9/L.

In our series, 1 case of bone marrow fibrosis was reported, leading to treatment discontinuation and subsequent recovery. Bone marrow fibrosis is reported with other TPO-RAs at low frequency (≥ 1/1,000 to < 1/100), and to date, it has always been reversible upon discontinuation of the agonist. Some authors[27] recommend avoiding starting treatment with agonists if the patient develops reticulin deposits in the bone marrow (European Consensus MF-2 to MF-3), and any TPO-RA should be avoided until these deposits and associated clinical symptoms resolve.

The possibility of discontinuing avatrombopag was not possible in our case, unlike what has been reported with other agonists. A priori, same as other agonists[28], avatrombopag may have an immunomodulatory effect associated with fewer helper T cell effector functions. It is known that other agonists are associated with continuous activation of the JAK/STAT signaling pathway, which could cause prolonged response; this activation is also observed with avatrombopag[29]. Therefore, after achieving hemostatic platelet counts, some patients may show a sustained response after discontinuing avatrombopag. In our registry, 7/53 patients maintain a platelet count ≥ 100 × 10^9/L with a weekly dose ≤ 60 mg (mean, 42.85 mg) and are in the process of tapering to discontinuation.

Conclusions

Avatrombopag has proven effective and safe in our patients with chronic ITP and newly diagnosed ITP. We highlight:

- Efficacy and rapid response.
- Convenience of oral administration, avoiding the disadvantages of subcutaneous administration and the need (in many cases) to visit the hospital for treatment administration.
- No dietary restrictions, especially in elderly patients with frequent dietary restrictions, as food or divalent cations do not affect absorption, avoiding the need for fasting, leading to greater patient independence.
- No need for liver function monitoring.

All these aspects make avatrombopag very attractive. The drug tolerability is very good, with generally mild and easily manageable side effects and a low incidence of VTE; only 1 case in our registry and 0 in the AVAMAD trial, figures that do not seem to justify special measures in these patients. It will probably be necessary to emphasize controlling cardiovascular risk factors to minimize this risk, and even consider antiplatelet or prophylactic anticoagulation because the benefit-risk ratio of avatrombopag use is very high. Of note that it is the only TPO-RA indicated for ITP and chronic liver disease. Although the success of avatrombopag in this indication in chronic liver disease is highly dependent on adequate surgical scheduling and good inter-service coordination, it can offer a significant advantage over platelet transfusions in terms of transfusion safety, expenses, and managing a resource highly dependent on a fluctuating donor population.

The financial aspect is also interesting. Although highly variable by hospital, switching to avatrombopag can save treatment costs in some patients and centers, as fewer doses are often required to maintain a safe platelet count than would proportionally be needed from other agonists. In line with Virk et al.[16], the potential use of TPO-RAs, in this case, avatrombopag, as first-line therapy is very promising. However, there are gaps, such as whether we will be able to induce remissions in newly diagnosed ITP similarly to what is observed with corticosteroids, and other questions, but our experience encourages us to think so.

Controlled clinical trials should be conducted to establish an indication for TPO-RAs as first-line therapy in newly diagnosed ITP in the future. Although our sample size does not allow us to draw definitive conclusions, avatrombopag seems to be the optimal second-line therapy for adult ITP, which is consistent with what other authors have expressed[30,31], achieving the highest efficacy with the most favorable balance of benefits and acceptability[31].

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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References

1. AEMPS. Ficha técnica de avatrombopag. (Consultado el 6-4-2024.) Disponible en: https://cima.aemps.es/cima/dochtml/ft/1191373/FT_1191373.html.
2. Terrell DR, Terrell R, Beebe LA, Vesely SK, Neas BR, Segal_JB, et al. The incidence of immune thrombocytopenic purpura in children and adults: a critical review of published reports. Am J Hematol. 2010;85:174-80.
3. Schoonen WM, Kucera G, Coalson J, Li L, Rutstein M, Mowat F, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. Br J Haematol. 2009;145:235-44.
4. Pascual Izquierdo C, Canaro Hirnyk M, Sánchez González B, Mingot Castellano ME, coordinadoras. Recomendaciones del GEPTI para el diagnóstico y tratamiento de la trombocitopenia inmune. Sociedad Española de Hematología y Hemoterapia (SEHH); 2023. Disponible en: file:///C:/Users/ccomp/Downloads/GUIA-GEPTI-2023.pdf.
5. López MR, López-Ansoar E, Iglesias-Varela R, Domínguez-Muñiz O, Albo-López C. Avatrombopag and CLD: about a patient with severe haemophilia A. Sangre. 2023;42:99-102.
6. Sociedad Española de Transfusión Sanguínea y Terapia Celular. Guía SETS sobre la transfusión de componentes sanguíneos y derivados plasmáticos. 5.ª ed. Barcelona: SETS; 2015. Disponible en: https://sets.es/images/site/guias/GuiaTransfusión_5º_EDICION_2015.pdf
7. Mingot-Castellano ME, Canaro Hirnyk M, Sánchez-González B, Álvarez-Román MT, Bárez-García A, Bernardo-Gutiérrez A, et al. Recommendations for the clinical approach to immune thrombocytopenia: Spanish ITP Working Group (GEPTI). J Clin Med. 2023;12:6422.
8. Lambert C, Maitland H, Ghanima W. Risk-based and individualised management of bleeding and thrombotic events in adults with primary immune thrombocytopenia (ITP). Eur J Haematol. 2024;112:504-15.
9. Gómez-Almaguer D, Rojas-Guerrero EA, Gómez-De León A, Colunga-Pedraza PR, Jaime-Pérez JC. Alternatives for managing patients with newly diagnosed immune thrombocytopenia: a narrative review. Expert Rev Hematol. 2022;15:493-501.
10. Jurczak W, Chojnowski K, Mayer J, Krawczyk K, Jamieson BD, Tian W, et al. Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol. 2018;183:479-90.
11. Al-Samkari H, Nagalla S. Efficacy and safety evaluation of avatrombopag in immune thrombocytopenia: analyses of a phase III study and long-term extension. Platelets. 2022;33:257-264.
12. Tarantino MD, Vredenburg M, Tian W, Jamieson B, Patel KB. Efficacy analyses from the immune thrombocytopenia (ITP) clinical development program for avatrombopag: comparisons with placebo and eltrombopag [abstract]. Blood. 2020;136(Suppl 1):23-4.
13. Llácer Ferrandis MJ, Monsalvo Saornil S, De Laiglesia A, Martínez Vázquez C, Menor Gómez M, Chica Gullón E. Avatrombopag in immune thrombocytopenia (ITP). Real-life experience of its use in hospitals within the Community of Madrid, Spain (AVAMAD study). Blood. 2023;142(Suppl 1):3961.
14. Al-Samkari H, Jiang D, Gernsheimer T, Liebman H, Lee S, Wojdyla M, et al. Adults with immune thrombocytopenia who switched to avatrombopag following prior treatment with eltrombopag or romiplostim: a multicentre US study. Br J Haematol. 2022;197:359-66.
15. Calviño-Suárez M, López Ansoar E, Lorenzo Vizcaya A, Guzmán Fernández MR, Dorado López A, Salido Toimil F, et al, Galician experience with avatrombopag: Galician Thrombosis and Hemostasis Group. Blood. 2023;142(Suppl 1):5446.
16. Virk ZM, Leaf R, Kuter D, Goodarzi K, Connell N, Connors JM, et al. Avatrombopag for adults with early versus chronic immune thrombocytopenia. Am J Hematol. 2024;99:155-62.
17. Takagi S, Suzuki I, Watanabe S. Risk of thromboembolism in patients with immune thrombocytopenia. J Hematol Thromb Dis. 2015;3:185.
18. Palandri F, Rossi E, Bartoletti D, Ferretti A, Ruggeri M, Lucchini E, et al, Real-world use of thrombopoietin receptor agonists in older patients with primary immune thrombocytopenia. Blood. 2021;138:571-83.
19. Justo Sanz R, Monzón Manzano E, Fernández Bello I, Álvarez Román MT, Martín Salcés M, Rivas Pollmar MI, et al. Platelet apoptosis and PAI-1 are involved in the pro-coagulant state of immune thrombocytopaenia patients treated with thrombopoietin receptor agonists. Thromb Haemost. 2019;119:645-59.
20. Lozano ML, Garabet L, Fernández-Pérez MP, De Los Reyes-García AM, Díaz-Lozano P, García-Barbera N, et al. Platelet activation and neutrophil extracellular trap (NET) formation in immune thrombocytopenia: is there an association? Platelets. 2020;31:906-12.
21. Swan D, Newland A, Rodeghiero F, Thachil J. Thrombosis in immune thrombocytopenia — current status and future perspectives. Br J Haematol. 2021;194:822-34.
22. Provan D, Thachil J, Álvarez Román MT. Addressing thrombosis concerns in immune thrombocytopenia: the role of fostamatinib in immune thrombocytopenia management. Expert Rev Hematol. 2024;17:55-66.
23. García Ortega A, Jiménez D, Pedro-Tudela A, Pérez-Ductor C, Fernández-Capitán C, Falgá C, et al. Age-related differences in the presentation, management, and clinical outcomes of 100,000 patients with venous thromboembolism in the RIETE Registry. Arch Bronconeumol. 2024;60:143-52.
24. Rodoghiero F. Is ITP a thrombophilic disorder? Am J Haematol. 2016; 91:39-45.
25. González López TJ, Jarque Ramos I, coordinadores. Resultados del Consenso Delphi. Recomendaciones PTI. Evaluación de la práctica clínica habitual en España ante la llegada de nuevos fármacos para el tratamiento de la PTI. Disponible en: file:///C:/Users/ccomp/Downloads/Slide-Kit-Resultados-Consenso-Delphi-PTI.pdf.
26. Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. Haematologica. 2019;104:1112-23.
27. González-Porras JR, Godeau B, Carpenedo M. Switching thrombopoietin receptor agonist treatments in patients with primary immune thrombocytopenia. Ther Adv Hematol. 2019;10:2040620719837906.
28. Bao W, Bussel JB, Heck S, He W, Karpoff M, Boulad N, et al. Improved regulatory T-cell activity in patients with chronic immune thrombocytopenia treated with thrombopoietic agents. Blood. 2010;116:4639-45.
29. Kuter DJ. Biology and chemistry of thrombopoietic agents. Semin Hematol. 2010;47:243-8.
30. Liu Y, Zhang HX, Su J, Geng QC, Lin X, Feng CX. Efficacy and incidence of treatment related adverse events of thrombopoietin receptor agonists in adults with immune thrombocytopenia: a systematic review and network meta-analysis of randomized controlled study. Acta Haematol. 2023;146:173-84.
31. Deng J, Hu H, Huang F, Huang C, Huang Q, Wang L, et al. Comparative efficacy and safety of thrombopoietin receptor agonists in adults with thrombocytopenia: a systematic review and network metaanalysis of randomized controlled trial. Front Pharmacol. 2021;12:704093.

Hemostasia y Trombosis
REVISTA IBEROAMERICANA DE TROMBOSIS Y HEMOSTASIA

ORIGINAL ARTICLE

Utility of phospholipid-sensitive and insensitive APTT pairs together with dRVVT in the diagnosis of lupus anticoagulant

Utilidad de pares de APTT sensible e insensible a fosfolípidos junto al dRVVT en el diagnóstico de anticoagulante lúpico

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Abstract

Introduction and objective: *Laboratory diagnosis of antiphospholipid syndrome (APS) requires the determination of lupus anticoagulant (LA) activity by coagulation assays and antiphospholipid antibodies by solid-phase assays. Despite the years that have passed, the diagnosis of LA is still complex and requires well-established coagulation methods, properly obtained cut-off points and professional judgment for the interpretation of the results.* **Method:** *Two types of specific assays for LA based on different principles: dRVVT (dilute Russell's viper venom time) and sensitive APTT are recommended for the detection of LA. This is complemented by mixing assays with normal plasma and confirmatory assays. One of the interpretations is based on the calculation of the detection assay/confirmatory assay ratio. In an attempt to resemble the dRVVT detection/confirmatory assay, various combinations have recently been proposed using APTT with low or high sensitivity to phospholipids. In two centres (one with optical coagulometer and another with mechanical detection) we used PTT-LA as sensitive APTT and Pathromtin-SL and CK-Prest as insensitive APTTs.* **Results:** *Based on locally established cut-off points, in centre A 50 patients were positive for AL out of 173 evaluated. In centre B there were 36 positives out of 130 patients. In both centres the combination of paired APTTs (sensitive/insensitive) PTT-LA/Pathromtin or PTT-LA/CK-Prest demonstrated high sensitivity to detect AL.* **Conclusions:** *This strategy proved to be useful and economical for the diagnosis of AL according to current international standards.*

Keywords: *Lupus anticoagulant. APTT. Antiphospholipid syndrome.*

Resumen

Introducción y objetivo: *El diagnóstico de laboratorio del síndrome antifosfolípido (SAF) requiere la determinación de la actividad de anticoagulante lúpico (AL) por ensayos de coagulación y de anticuerpos antifosfolípidos por ensayos en fase sólida. A pesar de los años transcurridos el diagnóstico del AL siempre resulta complejo y requiere métodos de coagulación bien esTablecidos, puntos de corte adecuadamente obtenidos y criterio profesional para la interpretación de los resultados.* **Método:** *Dos tipos de ensayos específicos para AL basados en principios diferentes: dRVVT (tiempo de veneno de víbora Russell diluido) y APTT sensible son los recomendados para la detección del AL. Se complementa con ensayos de mezcla con plasma normal y con ensayos confirmatorios. Una de las interpretaciones se basa en el cálculo de la razón del ensayo de detección/ensayo de confirmación. Intentando semejarse al ensayo dRVVT detección/confirmatorio se han propuesto*

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recientemente diversas combinaciones usando APTT con baja o alta sensibilidad a los fosfolípidos. En dos centros (uno con coagulómetro óptico y el otro con detección mecánica) utilizamos PTT-LA como APTT sensible y como APTT insensible al Pathromtin-SL y CK-Prest. **Resultados:** *Basados en puntos de corte esTablecidos localmente, en el centro A se hallaron 50 pacientes positivos para AL de 173 evaluados. En el centro B hubo 36 positivos de 130 pacientes. En ambos centros la combinación de APTT apareados (sensible/insensible) PTT-LA/Pathromtin o PTT-LA/CK-Prest demostraron alta sensibilidad para detectar AL.* **Conclusiones:** *Esta estrategia resultó ser útil y económica para el diagnóstico de AL de acuerdo con las normas internacionales vigentes.*

Palabras clave: *Anticoagulante lúpico. APTT. Síndrome antifosfolípido.*

Introduction

The laboratory diagnosis of antiphospholipid syndrome (APS) requires the determination of lupus anticoagulant (LA) activity through coagulation assays, and anticardiolipin and anti-β2-glycoprotein I antibodies via solid-phase assays[1]. LA detection is based on phospholipid (PL)-dependent coagulation assays. Despite advancements over the years, diagnosis remains complex, requiring well-established coagulation methods, accurately derived cut-off values, and professional expertise in result interpretation. Additional challenges arise in evaluating patients on anticoagulant therapy with heparin, vitamin K antagonists, and direct oral anticoagulants (DOACs) targeting factor Xa and antithrombin.

The latest guidelines, published in 2020 by the Scientific Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH)[2], outline a series of recommendations for laboratories conducting LA testing. These guidelines recommend a systematic profile of baseline assays (prothrombin time, standard APTT, and thrombin time) to assess the patient's baseline status. Additionally, two specific types of LA assays based on different principles are recommended: dRVVT (dilute Russell's viper venom time) and a sensitive APTT with low PL concentration. APTT should preferably use silica as the activator since, while ellagic acid shows some sensitivity, it is less sensitive than silica. Detection assays are considered prolonged (one or both) when the result exceeds the locally established cut-off in each laboratory after assessing normal plasma samples. The guidelines recommend reporting the patient/normal ratio. If the detection assay is prolonged, mixing studies with normal plasma and confirmatory assays are performed for the affected test[2]. One interpretation approach is based on calculating the (normalized or unnormalized) ratio of the detection assay/confirmation assay. This result is considered positive if the ratio exceeds the 99th percentile of the normal distribution.

Cut-off points should be established by evaluating normal plasmas over several days, with a recommendation of using 100–120 plasmas from apparently normal individuals[3]. Reference ranges for normality should be established between the 2.5th and 97.5th percentiles, while the cut-off for positivity is suggested to be the 99th percentile (P_{99}) of the distribution; thus, a test is positive when it exceeds the locally established cut-off. This applies to individual assays as well as to the ratios used (e.g., screen/confirm, patient+normal/normal, etc.). Outliers (values at the extremes of the normal distribution) should be excluded before establishing normal cut-offs[2]. The Reed method is recommended for this purpose, primarily involving the exclusion of the longest result (in the case of LA assays).

CLSI (Clinical and Laboratory Standards Institute) guidelines H60 recommend conducting mixing and confirmatory assays simultaneously, and in the absence of another coagulopathy, if the confirmatory test is above the cut-off, LA is considered positive even if the sample corrects with a normal pool[4]. In this guideline, assay cut-offs are set at the 97.5th percentile (P97.5th).

The recommended methods for LA detection or screening are limited to two types: dRVVT and APTT with low PL concentration (Table 1). This combination provides a high probability of detecting LA if present. Another widely used commercial assay globally is the silica clotting time (SCT), which is essentially an APTT with silica as the activator. A recently validated assay for LA assessment utilizes two snake venoms that directly activate prothrombin[5]: the Taipan venom time, which is PL-sensitive and unaffected in patients on vitamin K antagonists or anti-FXa DOACs, and the Ecarin time, which is PL-insensitive and serves as the confirmatory test (Table 1).

In certain regions where SCT has not been approved by regulatory agencies for laboratory use, various combinations involving APTT with both high and low PL sensitivity have been proposed recently[6-9]. In recent years, paired APTTs (sensitive/insensitive) have become increasingly popular for LA diagnosis due to their low cost.

Method

Population

Consecutive patients admitted to services for AL evaluation and who signed informed consent. In some cases, this was within the context of thrombophilia studies due to a history of venous and/or arterial thrombosis (center A: *n* = 65, center B: *n* = 71); in other cases, it was due to the presence of autoimmune diseases (center A: *n* = 49, center B: *n* = 20), a history of obstetric morbidity (center A: *n* = 41, center B: *n* = 20), or simply because they had prolonged APTT results in routine tests (center A: *n* = 18, center B: *n* = 19). Patients diagnosed with acquired hemophilia and those with factor deficiencies:

– Center A: 100 normal plasmas (blood donors) collected on different days were used to establish the reference range for each APTT reagent used, and the cutoff was set at the 99th percentile for the APTT sensitive/APTT insensitive ratios. The APTT reagents tested were PTT-LA (Diagnostica Stago) as APTT sensitive, and Pathromtin-SL (Siemens) and CK-Prest (Diagnostica Stago) as APTT insensitive. The PTT-LA activator is silica, the Pathromtin activator is silicon dioxide, and the CK-Prest activator is kaolin. Additionally, the cutoff (P_{99}) was established for the dRVVT screen (LA1, Siemens), dRVVT confirm (LA2, Siemens), and the dRVVT screen/confirm ratio.

These assays were evaluated simultaneously (APTT and dRVVT) in 173 patients referred for AL studies, using the dRVVT screen and confirm assay, and PTT-LA for initial diagnosis. All tests were performed on an automated BCSXP coagulation analyzer (Siemens) using an optical detection method.

– Center B: a total of 120 normal plasmas were used to establish the reference range for each APTT reagent, and the cutoff was evaluated at the 97.5th and 99th percentiles for the APTT sensitive/APTT insensitive ratios. The APTT reagents tested were PTT-LA as APTT sensitive and Pathromtin-SL and CK-Prest as APTT insensitive.

A total of 130 patients were referred for AL evaluation, and for the initial diagnosis, the dRVVT screen and confirm assay (Diagnostica Stago) and the SCT screen and confirm (Werfen) were used. In cases in which the SCT tested positive (*n* = 36), all 3 APTT assays were tested on the same day or within 4 hours of sample collection. All coagulation assays were performed on an automated STA-Compact Max 3 (Diagnostica Stago) using a mechanical detection method.

Table 1. Tests and combinations used in lupus anticoagulant diagnosis

	LA-sensitive test	LA-non-sensitive test
dRVVT (paired)	dRVVT screen (Werfen-Stago-Siemens-TCoag)	dRVVT confirm
APTT (paired)	SCT screen (Werfen)	SCT confirm
	PTT-LA (Stago)	Staclot LA (kit)
	PTT-LA (Stago)	CK-Prest
	PTT-LA (Stago)	Pathromtin-SL (Siemens)
	Cephen LS (Hyphen)	Cephen
	Actin FSL (Siemens)	Actin FS (Siemens)
T/E	Taipan test	Ecarin test

APTT: activated partial thromboplastin time; dRVVT: dilute Russell's viper venom time; LA: lupus anticoagulant; PTT-LA: commercial name for APTT; SCT: silica clotting time; T/E: Taipan/Ecarin.

None of the patients in either center were on anti-vitamin K, DOAC, or heparin therapy.

Both centers also evaluated the results of different APTT ratios in samples from patients with acquired hemophilia and in in vitro factor-deficient plasmas (factors VIII, IX, and XI).

Factor activity was determined using a 1-stage clotting method at three dilutions with factor-deficient Stago plasmas.

Factor-deficient samples were prepared by mixing different volumes of factor-deficient plasma with a normal plasma pool. The activity of each factor was determined by the clotting method mentioned above.

Statistics

Percentiles of the normal distribution were obtained using traditional statistical methods, and concordance between assays was assessed using the kappa coefficient.

Results

Center A

The normal cutoff (P_{99}) for the PTT-LA/CK-Prest ratio was 1.30, and for the PTT-LA/Pathromtin ratio, 1.31.

For the dRVVT screen/confirm ratio, the cutoff was set at 1.35 on the BCS-XP device.

A total of 50 (28.9%) out of the 173 patients studied tested AL positive. There were 21 cases (42%) with both ratios (dRVVT and APTT) positive, 16 (32%) with only the dRVVT ratio positive, and 13 (26%) with only the APTT PTT-LA/Pathromtin ratio positive (Table 2). Using the PTT-LA/CK-Prest combination, results were similar: 22 cases (44%) positive with both assays, 17 (34%) positive with only dRVVT, and 11 (22%) with only the PTT-LA/CK-Prest ratio positive.

The concordance level between the established method (dRVVT and PTT-LA) and the APTT sensitive/insensitive ratio, as measured by kappa correlation coefficients, was PTT-LA/Pathromtin 0.74 (95% confidence interval [CI], 0.96-0.49) and PTT-LA/CK-Prest 0.71 (95%CI, 0.93-0.46).

Overall, the dRVVT screen/confirm ratio tested positive in 74-78%, the PTT-LA/Pathromtin ratio in 68%, and the PTT-LA/CK-Prest ratio in 66% of AL-positive patients. Among AL-positive samples, the PTT-LA/Pathromtin ratio ranged from 1.47-4.05, the PTT-LA/CK-Prest ratio from 1.41-3.14, and the dRVVT screen/confirm ratio from 1.41-2.89.

Center B

The normal cutoff ($P_{97.5}$ and P_{99}) for the PTT-LA/Pathromtin ratio was 1.39 and 1.59, respectively. For the PTT-LA/CK-Prest ratio, the values were 1.50 and 1.62. For the dRVVT screen/confirm ratio, the cutoff was set at 1.20 ($P_{97.5}$) on the Compact Max device.

In both tests, 69 patients tested negative; 61 patients tested positive for AL: 27 positive in both SCT and dRVVT, 25 positive only in dRVVT, and 9 positive only in SCT.

The kappa correlation coefficient for concordance between the established method (SCT) and the APTT sensitive/insensitive ratio was: PTT-LA/Pathromtin 0.60 (95%CI, 0.81-0.38) and PTT-LA/CK-Prest 0.63 (95%CI, 0.85-0.42) at P_{99}, and PTT-LA/Pathromtin 0.77 (95%CI, 1.00-0.54) and PTT-LA/CK-Prest 0.75 (95%CI, 0.98-0.57) at $P_{97.5}$.

Using the combination of dRVVT and APTT ratios (including both tested combinations) with $P_{97.5}$ (for better kappa values), there were 27 cases (75%) with both ratios (dRVVT and APTT) positive and 8 (22%) with only the APTT ratio positive (Table 2).

Among AL-positive samples, the PTT-LA/Pathromtin ratio ranged from 1.42-2.92, the PTT-LA/CK-Prest ratio from 1.52-2.43, and the dRVVT screen/confirm ratio from 1.24-2.63.

Table 2. Distribution of results in the two evaluated centers. The table shows the number of patients with positive and negative results for the dRVVT ratio and/or APTT ratio. In center A, PTT-LA/Pathromtin was used, and in center B, two combinations of PTT-LA and P97.5 were applied

Center A	dRVVT ratio (+)	dRVVT ratio (–)	
APTT ratio (+)	21	13	34
APTT ratio (–)	16	123	139
Total	37	136	173
Center B	**dRVVT ratio (+)**	**dRVVT ratio (–)**	
APTT ratio (+)	27	8	35
APTT ratio (–)	25	70	95
Total	52	78	130

APTT: activated partial thromboplastin time; dRVVT: dilute Russell's viper venom time.

In both centers, the APTT sensitive/insensitive ratios were negative in samples from patients with acquired hemophilia, congenital factor deficiencies, or in vitro factor-deficient samples with any APTT reagent combination tested (Tables 3 and 4).

Discussion

A crucial aspect of laboratory diagnosis for LA is the use of locally established cutoff points with no fewer than 100 normal plasma samples. These cutoffs can be defined at the 97.5th or 99th percentiles according to suggestions from international guidelines (CLSI or ISTH)[2,4]. In this study, the cutoff points obtained in both centers were significantly different despite using the same reagent combinations (PTT-LA/Pathromtin: center A, 1.31 vs. center B, 1.59; PTT-LA/CK-Prest center A, 1.30 vs. center B, 1.62). Cutoff points cannot be exchanged acros different laboratories or across different coagulometers within the same laboratory because the coagulometer detection system (optical or mechanical) significantly influences these definitions.

One of the earliest publications recommending a simple detection and confirmation assay is based on a 1997 report[6]. They used a rabbit brain cephalin and kaolin activator reagent as an APTT sensitive to LA, and Actin FS, containing plant-origin phospholipids (FL), as an LA-insensitive APTT. The ratio of the sensitive to insensitive APTT proved useful for detecting LA,

Table 3. Results of APTT sensitive/insensitive ratios in patients with inhibitors or congenital deficiencies (center A)

	PTT-LA/ Pathromtin ratio	PTT-LA/CK-Prest ratio
Anti-FVIII inhibitor 1	1.11	1.08
Anti-FVIII inhibitor 2	0.96	1.02
Anti-FVIII inhibitor 3	1.20	1.19
Anti-FIX inhibitor	0.96	1.05
FVIII 21%	1.03	1.08
FVIII 5%	1.10	1.15
FIX 29%	1.09	1.11
FIX 10%	1.12	1.16
FXI 11%	0.99	0.98
FXI 1%	1.10	1.12
FXII 25%	0.97	1.02
FXII 1%	1.09	1.05

Table 4. Results of APTT sensitive/insensitive ratios in patients with acquired deficiencies or deficiencies prepared *in vitro* (center B)

	PTT-LA/Pathromtin ratio	PTT-LA/CK-Prest ratio
Acquired HA 1	0.95	1.11
Acquired HA 2	0.78	1.17
Acquired HA 3	0.94	1.14
Acquired HA 4	0.87	1.16
FVIII 42%	0.99	0.99
FVIII 24%	0.96	0.96
FVIII 13%	0.96	0.96
FIX 37%	1.04	1.03
FIX 19%	1.14	1.11
FIX 7%	1.18	1.15
FXI 42%	1.00	0.98
FXI 24%	0.93	0.96
FXI 15%	0.95	1.02
FXII 40%	0.78	0.86
FXII 20%	0.83	0.91
FXII 10%	0.81	0.99

HA: hemophilia.

yielding normal results in patients on heparin and other hemostatic disorders that prolong the APTT. In 23 patients with LA, 22 had positive sensitive/insensitive APTT ratios (mean 2.08). They generally observed that results with the insensitive APTT were approximately half the time in seconds of those obtained with the sensitive APTT. In patients with factor deficiencies or anti-FVIII inhibitors, the ratios were close to 1.0 since prolongations were proportional across both reagents.

A different study compared the Cephen LS and Cephen APTT reagents[7]. The Cephen LS/Cephen ratio yielded positive results in 33 of 105 samples previously classified as LA-positive, with 31 also showing positive ratios using the dRVVT test (detection and confirmation). However, this reagent combination demonstrated lower sensitivity than previously obtained with the dRVVT ratio and PTT-LA as the sensitive APTT.

In 2016, a 4-year study in a pediatric center identified 161 patients with prolonged APTT, confirmed in a second sample[8]. They routinely used Platelin LS for its versatility in detecting both factor deficiencies and LA. As a confirmatory APTT for LA, they used Actin FS, an LA-insensitive reagent. The presence of LA was demonstrated in 64/88 (73%). Platelin LS (with silica) was prolonged in this patient group, and only 4 of the 64 patients showed prolongation with Actin FS. The established cutoff was 1.29, and the Platelin LS/Actin FS ratio demonstrated statistical significance with LA ($p < 0.05$). Using this pair of APTTs, sensitivity for LA detection increased to 82-86%.

In Switzerland, a study aimed to determine whether using an LA-sensitive/insensitive APTT ratio could be a useful tool in LA testing[9]. They included samples from patients with factor deficiencies, anti-FVIII or anti-FIX inhibitors, and those on heparin or vitamin K antagonists. The primary group evaluated LA in 1553 patients over a 3-year period. They used Pathromtin-SL and PTT-LA, calculating the PTT-LA/Pathromtin-SL ratio in addition to dRVVT testing. The sensitivity of Pathromtin-SL for LA was 59%, PTT-LA was 82.1%, and the PTT-LA/Pathromtin-SL ratio was 92.3%.

Pathromtin-SL contains silica as an activator and plant-origin FL, while PTT-LA contains silica and cephalin. LA was identified in 78 out of the 1553 patients (5%), with the PTT-LA/Pathromtin-SL ratio cutoff established at 1.40. They demonstrated that calculating the ratio between clotting times obtained with the sensitive (PTT-LA) and less sensitive (Pathromtin) APTTs improved the performance of the PTT-LA and represented a simple, more cost-effective, and sensitive strategy based on the APTT assay.

The choice of CK-Prest was considered because it is a kaolin-based reagent with a high concentration of phosphatidylethanolamine. Thus, center A chose to use CK-Prest as the confirmatory APTT reagent for PTT-LA, which was our sensitive reagent for LA. The CK-Prest reagent has the disadvantage of requiring constant agitation, which is not efficiently achieved on our Siemens automated equipment, so manual shaking of the reagent was required for each use.

In both centers, the PTT-LA/Pathromtin combination yielded highly significant results for detecting LA and is now the combination used in our routine testing, consistent with findings from a different study[9].

Conclusions

The study and interpretation of LA still face certain challenges today due to the diversity of commercially available reagents with different sensitivities to LA, the lack of adherence by many laboratories to ISTH/CLSI guidelines, and the absence of local validation of cutoff points. These factors hinder the correct interpretation of LA presence or absence in test samples. Many laboratories only perform the dRVVT test, so the inclusion of paired APTTs (sensitive/insensitive) is very useful, as it complements the recommendations in international guidelines and offers a more economical option within the LA study panel.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have indeed used generative artificial intelligence, specifically ChatGPT-4, for the efficiency analysis of the 3 treatments, through the analysis of the results reported in the different studies.

References

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite anti-phospholipid syndrome (APS). J Thromb Haemost. 2006;4:295-306.
2. Devreese KMJ, de Groot PG, de Laat B, Erkan D, Favaloro EJ, Mackie I, et al. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2020;18:2828-39.
3. Favaloro EJ, Pasalic L. Lupus anticoagulant testing during anticoagulation, including direct oral anticoagulants. Res Pract Thromb Haemost. 2022;6:e12676.
4. Clinical and Laboratory Standards Institute. H60-A. Laboratory testing for the lupus anticoagulant; approved guideline [Internet]. Wayne, PA: Clinical and Laboratory Standards Institute; 2014. Disponible en: https://clsi.org/media/3402/h60ae_sample.pdf
5. Moore GW, Jones PO, Platton S, Hussain N, White D, Thomas W, et al. International multicenter, multiplatform study to validate Taipan snake venom time as a lupus anticoagulant screening test with ecarin time as the confirmatory test: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. J Thromb Haemost. 2021;19:3177-92.
6. Brancaccio V, Ames PR, Glynn J, Iannaccone L, Mackie I. A rapid screen for lupus anticoagulant with good discrimination from oral anticoagulants, congenital factor deficiency and heparin, is provided by comparing a sensitive and an insensitive APTT reagent. Blood Coagul Fibrinolysis. 1997;8:155-60.
7. Kumano O, Amiral J, Dunois C, Peyrafitte M, Moore GW. Paired APTTs of low and high lupus anticoagulant sensitivity permit distinction from other abnormalities and achieve good lupus anticoagulant detection rates in conjunction with dRVVT. Int J Lab Hematol. 2019;41:60-8.
8. Li R, Swaelens C, Vandermijnsbrugge B, Cantinieaux B. Applying a direct aPTT ratio (PlatelinLS/ActinFS) permits to identify rapidly and reliably a -related factor deficiency or a lupus anticoagulant sequential to an isolated prolongation of aPTT in paediatric pre-operative screening. Eur J Haematol. 2016;96:578-85.
9. Luginbühl R, Barizzi G, Sulzer I, Lammle B, Alberio L. Screening for lupus anticoagulant: improving the performance of the lupus-sensitive PTT-LA. Int J Lab Hematol. 2011;33:168-75.

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ORIGINAL ARTICLE

Prophylaxis in non-severe forms of hemophilia: experience of the HemoNorte working group

Profilaxis en formas no graves de hemofilia: experiencia del grupo de trabajo HemoNorte

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Abstract

Introduction: *Prophylaxis in mild and moderate hemophilia A has proven to be a fundamental pillar in managing the disease, significantly reducing bleeding episodes and improving patients' quality of life.* **Objective:** *To evaluate the efficacy of prophylaxis in 23 patients with mild-moderate hemophilia A and 10 patients with mild-moderate hemophilia B, comparing the results before and after switching to extended half-life concentrates.* **Method:** *Retrospective and observational study conducted by the HemoNorte group.* **Results:** *Previous studies have shown that even sporadic joint hemorrhages can lead to arthropathy and quality of life deterioration.This study underscores the importance of prophylaxis in preventing these long-term complications and the need for close monitoring to adjust treatment according to the patient's individual needs.* **Conclusions:** *The implementation of prophylaxis with extended half-life products offers multiple clinical and quality of life benefits for patients with mild to moderate hemophilia, justifying its continued and adapted use for each case.*

Keywords: *Prophylaxis. Non severe hemophilia. Anual bleeding rate.*

Resumen

Introducción: *La profilaxis en la hemofilia A leve y moderada ha demostrado ser un pilar fundamental en el manejo de la enfermedad, permitiendo reducir significativamente los episodios de sangrado y mejorando la calidad de vida de los pacientes.* **Objetivo:** *Evaluar la eficacia de la profilaxis en 23 pacientes con hemofilia A leve-moderada y en 10 pacientes con hemofilia B leve-moderada, comparando los resultados antes y después de cambiar a concentrados de vida media extendida.* **Método:** *Estudio retrospectivo y observacional realizado por el grupo HemoNorte.* **Resultados:** *Los estudios previos han*

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demostrado que incluso hemorragias articulares esporádicas pueden llevar a artropatías y deterioro de la calidad de vida. Este estudio subraya la importancia de la profilaxis para prevenir estas complicaciones a largo plazo y la necesidad de una monitorización estrecha para ajustar el tratamiento según las necesidades individuales de cada paciente. **Conclusiones:** *La implementación de la profilaxis con productos de vida media extendida ofrece múltiples beneficios clínicos y de calidad de vida a los pacientes con hemofilia leve-moderada, justificando su uso continuado y adaptado a cada caso.*

Palabras clave: *Profilaxis. Hemofilia no grave. Tasa anualizada de sangrado.*

Introduction

Prophylaxis in hemophilia is considered the treatment of choice for managing the disease, at least in patients classified as severe (plasma concentration of F8/F9 < 1 IU/dL)[1-3]. Its use in patients with other severity grades is less clear. Various studies in the scientific literature demonstrate that patients with mild and moderate hemophilia A or B suffer from joint bleeds, and some develop hemophilic arthropathy that may require surgical procedures. For this reason, the latest World Federation of Hemophilia guidelines[1] recommend prophylaxis even in moderate patients with a severe bleeding phenotype. The latest British clinical practice guidelines[2] recommend prophylaxis in hemophilic children with baseline factor levels of 1% up to 3%, and even consider it in hemophilic patients regardless of factor level, with recurrent hemarthroses or established arthropathy. Finally, the most recent and controversial guidelines from the International Society on Thrombosis and Hemostasis[3] recommend prophylaxis in severe and moderate hemophilia patients (strong recommendation based on moderate evidence). However, the use of prophylaxis in moderate and mild hemophilia patients in our setting has traditionally been low. The latest available data, from 2013,[4] reported that only 26.4% of moderate hemophilia A patients were on prophylaxis, mainly secondary (82.7%) at that time.

We present our group's experience on prophylaxis in this type of patient and how they have benefited from switching to extended half-life factor concentrates (EHL-CF) or other types of therapies.

The objective of this study is to report the experience and results of prophylaxis in patients with non-severe forms of hemophilia from the hospitals that make up the HemoNorte group, through the evaluation of annualized bleeding rates, total, spontaneous, and joint, comparing the results with previous on-demand treatment over a 24-month period (12 months before and 12 months after the start of prophylaxis).

Method

We conducted a retrospective, observational, and descriptive on patients with non-severe hemophilia A or B, without inhibitors, on prophylaxis with deficient factor concentrates (CFVIII/CFIX), before and after switching from standard half-life products to extended half-life products or others. These were patients of all ages, treated in the hematology departments of 9 hospitals from the National Health System, from 6 autonomous communities in northern Spain, all tertiary referral centers, without Reference Centers, Services, and Units (CSUR) designation.

The analysis covers the 12 months prior to the start of EHL-CF prophylaxis and the following 12 months. Data were collected from the patients' electronic health records. The main variables are the total annualized bleeding rate (ABR), spontaneous ABR, and joint ABR. Secondary variables include infusion frequency, weekly infused dose before and after the switch, achieved trough level, and adherence (number of infusions administered/number of infusions prescribed).

The results are expressed as percentage, mean and standard deviation, median and interquartile range. Statistical analysis was performed with Stata 14.

Results

Prophylaxis was evaluated in 23 patients with mild-to-moderate hemophilia A and the effect of switching to extended half-life CF8 (EHL-CF8) or other products. Patients without a past medical history of inhibitors or active inhibitors were included. The mutational study was available in 17 patients (73.9%). Blood type was available in 50% of patients, with type A being the most frequent (50%). Hemophilic arthropathy was present in 12 patients (48%). The mean age was 27.81 years (7-85 years), and 50% were younger than 18 years old. A total of 74% of patients had moderate hemophilia A (n = 17; mean plasma concentrations of F8 2.7% [1.2-4.8]) and 26% mild hemophilia A (n = 6, and mean plasma concentrations of F8 11.28% [6-25.7]). The mean von Willebrand factor activity (vWF RICO) (n = 21) was 95.88% (52-269%) (Table 1).

A total of 86.9% of hemophilia A patients were on previous prophylaxis (69.5% with standard half-life CF), and 13.04% on on-demand treatment. The most

Table 1. Patient characteristics

	Mild HA	Moderate HA	Mild HB	Moderate HB
Age > 18 years (n) (mean; SD)	4 (55; 24-85)	12 (13.25; 7-16)	2 (64; 55-73)	8 (41; 25-51)
Age < 18 years (n) (mean; SD)	2 (28; 12-16)	7 (41.14; 18-59)	0	1 (12)
Mutational status (n)	3	15	1	7
Previous treatment SHL-CF (n)	3 (N/A = 3)	17 (EHL-CF8: 2)	2	7
Dose (IU/kg/week) (mean; SD)	42.5 (35-50) (OD: 2 patients)	97.9 (50-187.5) (EHL: 87.5; 85.90)	0 (OD: 2 patients)	97.85 (50-105) (N/A: 1)
Frequency (days/week) (mean; SD)	2 (N/A: 2 patients)	2.93 (2-3.5) EHL: 2 (OD: 2 patients)	0	2.1 (1-3)
Switch to EHL-CF (n)	3 (SHL-CF8: 3)	12 (EMI: 1; SHL: 4; no switch: 2)	1 (SHL-CF9: 1)	9
Dose (IU/kg/week) (mean; SD)	50 (40-60) (SHL: 41.6; 25-50)	67.19 (33-100) (SHL: 73.75; 25-90)	45 (SHL: 100)	53.88 (50-60)
Frequency (mean; SD)	1.33 (1-2) (SHL: 1.66; 1-2)	1.85 (1.4-2.33) (EMI: 1; SHL: 2.75; 1-3)	2 (SHL: 1)	0.93 (0.7-1)

SD: standard deviation; EHL-CF: extended half-life factor concentrate; EMI: emicizumab; HA: hemophilia A; HB: hemophilia B; OD: on-demand; SHL-CF: standard half-life factor concentrate.

Table 2. Change in annualized bleeding rate (pre- and post-)

	F8/F9 (IU/dL) Mean (SD)	12 months PRE	Total ABR Mean (SD)	Spontaneous ABR Mean (SD)	Joint ABR Mean (SD)	12 months POST	Total ABR Mean (SD)	Spontaneous ABR Mean (SD)	Joint ABR Mean (SD)
Mild HA (n = 6)	11.28 (6-25)		2.4 (n = 5) (0-4)	0 (n = 5) (0-0)	2 (n = 5) (0-2)		0.83 (n = 6) (0-2)	0.33 (n = 6) (0-1)	0.66 (n = 6) (0-2)
Moderate HA (n = 19)	3.2 (1.2-5)		2.76 (0-4)	0.14 (0-2)	0.52 (0-2)		0.77 (0-2)	0 (0-0)	0.35 (0-2)
Non-severe HB (n = 11)	4.8 (2.1-6)		2.25 (0-3)	1.7 (0-3)	0.4 (0-2)		0.15 (0-2)	0 (0-0)	0.05 (0-1)

HA: hemophilia A; HB: hemophilia B; ABR: annualized bleeding rate.

common type of prophylaxis was secondary (58.8% in moderate hemophilia A and 66.6% in mild hemophilia A). Only 5 patients (25%) underwent pharmacokinetically guided prophylaxis.

The most common infusion regimen was 3 times a week (44% of patients). The mean weekly F8 consumption (n = 20) was 79.2 IU/kg (45.5-120). Reported adherence was > 90% in 70% of patients. The mean total ABR was 1.2, the mean spontaneous ABR was 0.25, and the mean joint ABR was 1.2 (Tables 1 and 2).

After the switch to CF8, 100% of patients were on prophylaxis, preferably with efmoroctocog alfa (26%) and simoctocog alfa (13%). The most frequent reason for the switch or initiation of prophylaxis was clinical in 47.8%, followed by physician or patient preference in 26.08%. One patient switched to emicizumab for clinical reasons. In those who switched to EHL-CF8 (n = 8), infusion frequency was reduced by approximately 50% (mean: 1.6/week) and weekly factor consumption by 27.86% (mean: 57.1 IU/kg). There was a significant reduction in total ABR, spontaneous ABR, and joint ABR to 0.4, 0.08, and 0.3, respectively. Adherence increased in 5 patients remaining the same (> 90%) in the rest (Tables 1 and 2).

Additionally, prophylaxis was evaluated in 10 patients with mild and moderate hemophilia B and the effect of switching to extended half-life CF9 (EHL-CF9). These were patients without a past medical history of inhibitors or active inhibitors. Mutational study was available in 90% of cases. Blood type was available in 80%, with type 0 being the most frequent (50%). A total of 70% of patients had hemophilic arthropathy. The mean age when the switch occurred was 41.3 years (12-73 years), with 90% of patients older

than 18 years. A total of 90% had moderate hemophilia B (mean plasma concentration of F9 4.5% [2.1-5]).

In the year prior to the switch, 80% were on prophylaxis, > 90% secondary, and none were guided by pharmacokinetics. A total of 100% used standard half-life recombinant CF9. The most widely used infusion regimen was twice a week (62.5%) (mean, 2.12/week). The mean weekly F9 consumption was 85.5 IU/kg (50-105). Reported adherence was > 90% in 87.5% of patients. The mean total ABR was 1.5; the mean spontaneous ABR, 0.4, and the mean joint ABR, 0.8 (Tables 1 and 2).

In the year after the switch to EHL-CF9, 100% of patients were on prophylaxis, preferably with eftrenonacog alfa (50%) and albutrepenonacog alfa (30%). The most common reason for the switch or initiation of prophylaxis was the physician or patient preference (in 100% of cases), and clinical reasons (in 90%). After the switch, the mean infusion frequency was 0.95/week (55% reduction) while weekly factor consumption was reduced by 35.2% (mean, 55.35 IU/kg). There was a significant reduction in total ABR, spontaneous ABR, and joint ABR to 0.3, 0, and 0.1, respectively. Adherence increased > 90% in 100% of patients (Tables 1 and 2).

Discussion

Most prospective clinical trials on prophylaxis in hemophilia are restricted to severe hemophilia, excluding patients with non-severe forms, in whom spontaneous bleeding is occasional, although prolonged bleeding due to trauma or minor surgical procedures may also be a common finding. Although the frequency of bleeding may be considered tolerable by patients with non-severe hemophilia, we must consider its mid- or long-term consequences, and thus pay attention to the implications for joint damage. The main factor affecting the loss of joint range of motion, apart from age, is known to be the factor level in plasma, and in this regard, the critical level seems to be around 10%[5]. We know that in hemophilia patients, 2 or 3 joint bleeds per year in the same joint can cause progressive and irreversible structural damage[6]. This fact negatively impacts the patients' quality of life. Indeed, the severity of joint deterioration is the main factor affecting the quality of life of patients with hemophilia A[6].

Numerous publications in the literature highlight that most moderate hemophilia A patients are not protected against joint damage[7]. It is important not to confuse baseline factor levels with target trough levels in prophylaxis. For example, while a moderate hemophilia A patient treated on-demand with a baseline F8 level of 2% is most of the time with factor levels < 5%, a severe hemophilia A patient on prophylaxis with a target trough level of 2% will be better protected, having most of the time F8 levels > 5%[7], benefiting from the protection associated with peak levels and the larger area under the curve characteristic of prophylaxis regimens with factor concentrate.

In the PROBE trial[8], with 134 moderate hemophilia patients, only 35% were on continuous prophylaxis, despite 82% having an ABR ≥ 2-3. Bleeds caused joint damage in patients, resulting in 74.42% having joints with compromised range of motion and 70% needing some type of mobility aid. Additionally, 77.3% of moderate hemophilia A patients reported acute pain and 71.4% chronic pain, with only 12.8% not requiring analgesia for pain control. These data reflect a considerable impact of the disease on quality of life, as 61.6% of patients reported difficulties performing activities of daily living. This evidence confirms that most moderate (and, also, mild) hemophilia A patients are not protected against joint damage, thus experiencing a deterioration in their quality of life.

In 2021, De la Corte et al.[9] evaluated arthropathy in 6 typical target joints (ankles, knees, and elbows) in 28 adult hemophilia A patients (mean age, 42.5 years), 14 of whom had moderate disease and 14 only mild. Of all the patients, 22 were on-demand treatment. Analyses included evaluating patients with the HEAD-US (Haemophilia Early Arthropathy Detection with Ultrasound) scoring system. The authors recorded a HEAD-US score of 0 in all joints in 5 mild hemophilia patients (37.5%) and 3 moderate hemophilia patients (21.4%). Eight patients showed damage in, at least, 1 target joint, suggesting delayed damage detection and thus suboptimal prevention of possible joint damage in these patients. Based on the HEAD-US score obtained, the authors decided to switch to prophylaxis in 25% of mild patients and 33% of moderate patients. The study concluded that arthropathy could also be detected in mild and moderate patients. Therefore, in the non-severe hemophilia A scenario, it is equally crucial to carry out proper joint damage prevention. Additionally, the importance of close monitoring for these patients is highlighted, with regular ultrasound reviews of the 6 target joints as a guide for treatment decision-making. Similar conclusions were reached by other studies, such as the one conducted by Mohem[10] and Dynamo[11].

One weakness of our work, besides the small sample size, is the absence of joint assessment using HEAD-US, as it is not universally implemented in our centers, although efforts are being made for its progressive incorporation as a measure not only to evaluate joint health but also treatment efficacy and as a tool

to implement personalized prophylaxis. Despite a reduction in ABR of any type (total, spontaneous, and joint), which, although low before the switch, decreases after the transition to EHL-CF in hemophilia A or B patients, the use of joint ultrasound as a marker of subclinical joint damage is important to evaluate prophylaxis efficacy and guide therapeutic decision-making.

Additionally, the advantages associated with using extended half-life products[1] in terms of reduced infusion frequency, which can result in higher treatment adherence, or increased trough levels, translating to greater bleed protection, are known. In our series, after the switch, infusion frequency reduction was 50% in hemophilia A patients and up to 55% in hemophilia B patients, which likely contributed to the observed increase in treatment adherence in many patients. At the same time, a reduction in factor consumption of 27.86% for hemophilia A and 35.2% for hemophilia B was observed after the switch to EHL-CF, without compromising clinical prophylaxis results.

Conclusions

Our work demonstrates that extending prophylaxis to mild-to-moderate hemophilia patients represents a fundamental pillar in the management of this condition, significantly reducing bleeds and improving these patients' quality of life. With well-structured prophylaxis, it should be possible to prevent or delay complications such as hemophilic arthropathy and improve these patients' daily functionality.

Using extended half-life concentrates offers multiple advantages in hemophilia prophylactic treatment, which can translate to greater convenience and treatment adherence by patients, as observed in those with severe hemophilia. Additionally, these concentrates have demonstrated comparable or superior efficacy in bleeding prevention, providing prolonged and sustained protection with less frequent dosing. This improvement in pharmacokinetics optimizes clinical outcomes and reduces treatment burden, which is particularly beneficial for younger patients and their families, facilitating full integration into their daily activities.

In conclusion, prophylaxis in mild-to-moderate hemophilia patients, especially with the incorporation of extended half-life products or other treatment modalities, represents a significant advancement in managing this disease, providing substantial clinical and quality-of-life benefits that justify its implementation and continuity.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe WS, et al. WFH Guidelines for the management of hemophilia, 3rd edition. Haemophilia. 2020;26(Suppl 6):1-158.
2. Rayment R, ChalmersE, Forsyth K, Gooding R, Kelly AM, Shapiro S; British Society for Haematology, Guidelines on the use of prophylactic factor replacement for children and adults with haemophilia A and B. Br J Haematol. 2020;190:684-95.
3. Rezende SM, Neumann I, Angchaisuksiri P, Awodu O, Boban A, Cuker A, et al. International Society on Thrombosis and Haemostasis clinical practice guideline for treatment of congenital hemophilia A and B based on the GRADE methodology. J Thromb Haemost. 2024; 1-58. In press. Disponible en: https://doi.org/10.1016/j.jtha.2024.05.026.
4. Aznar JA, Altisent C, Álvarez-Román MT, Bonanad S, Mingot-Castellano ME, López MF. Moderate and severe haemophilia in Spain: an epidemiological update. Haemophilia. 2018;24:e136-9.
5. Wang M, Recht M, Iyer NN, Cooper DJ, Soucie M. Hemophilia without prophylaxis: assessment of joint range of motion and factor activity. Res Pract Thromb Haemost. 2020;4:1035-45.
6. Gringeri A, Ewenstein B, Reininger A. The burden of bleeding in haemophilia: ¿is one bleed too many? Haemophilia. 2014;20:459-63.
7. Collins PW, Obaji SG, Roberts H, Gorsani D, Rayment R. Clinical phenotype of severe and moderate haemophilia: ¿who should receive prophylaxis and what is the target trough level? Haemophilia. 2021;27:192-8.
8. Chai-Adisaksopha C, Noone D, Curtis R, Frick N, Nichol MB, Germini F, et al. Non-severe haemophilia: is it benign? Insights from the PROBE study. Haemophilia. 2021;27(Suppl 1):17-24.
9. De la Corte-Rodríguez H, Rodríguez-Merchán EC, Álvarez-Román MT, Martín-Salces M, Rivas-Pollmar I, Jiménez-Yuste V. Arthropathy in people with mild haemophilia: exploring risk factors. Thromb Res.2022;211:19-26.
10. Ragnhild J. M, Berntorp E, Astermark J Olsson A, Bruzelius M, Frisk T et al.Joint health and treatment modalities in Nordic patients withmoderate haemophilia A and B – The MoHem studY. Haemophilia. 2020;26:891–897.DOI: 10.1111/hae.14114.
11. Kloosterman F, Zwagemaker A.F, Bay-Jensen A.C, Cnossen M, Kruip M, Leebeek F et al, Poor correlation between biomarkers and MRI-detected joint damage in a cross-sectional study of persons with nonsevere hemophilia A (DYNAMO study) Journal of Thrombosis and Haemostasis (2023) 21 (7) 1813-1823, https://doi.org/10.1016/j.jtha.2023.03.030.

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REVIEW ARTICLE

Indirect comparison of two real-life studies in immune thrombocytopenia using artificial intelligence

Comparación indirecta de dos estudios en la vida real en trombocitopenia inmune con uso de inteligencia artificial generativa

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Abstract

Artificial intelligence (AI) is here to stay in medicine. This paper explores the use of generative AI tools (ChatGPT4o and Perplexity AI) to compare the efficacy and safety of two new drugs for chronic primary immune thrombocytopenia (ITP), fostamatinib and avatrombopag, using data from real-life studies. The comparison aims to aid in treatment selection for adult patients with ITP who have not responded to previous treatments. Both treatments are effective and safe, but avatrombopag shows a higher response rate and lower incidence of common adverse events. The choice of treatment may depend on additional clinical factors, patient preferences and economic considerations. ChatGPT4o suggests an initial economic advantage for fostamatinib, while Perplexity AI favours avatrombopag in the long term in the Spanish setting. It is concluded that AI can be a valuable tool for treatment comparison, but validation and human oversight are essential to ensure the quality of the information generated. The analysis suggests that both therapeutic options are valid for the management of patients with chronic ITP, highlighting the importance of a collaborative approach between AI and haematologists to maximise outcomes.

Keywords: *Inmune thrombocytopenia. Artificial intelligence. Real life.*

Resumen

La inteligencia artificial (IA) ha llegado a la medicina para quedarse. Este artículo explora el uso de herramientas de IA generativa (ChatGPT4o y Perplexity AI) para comparar la eficacia y la seguridad de dos nuevos fármacos para la trombocitopenia inmunitaria primaria (también conocida como púrpura trombocitopénica idiopática [PTI]) crónica, el fostamatinib y el avatrombopag, utilizando datos de estudios en la vida real. La comparación pretende ayudar en la selección del tratamiento para pacientes adultos con PTI que no han respondido a tratamientos previos. Ambos fármacos son eficaces y seguros, pero el avatrombopag muestra una mayor tasa de respuesta y menor incidencia de eventos adversos comunes. La elección puede depender de factores clínicos adicionales, las preferencias del paciente y consideraciones económicas. ChatGPT4o sugiere una ventaja económica inicial para el fostamatinib, mientras que Perplexity AI favorece al avatrombopag a largo plazo en el contexto español. Se concluye que la IA puede ser una herramienta valiosa para la comparación de tratamientos, pero la validación y la supervisión humana son esenciales para garantizar la calidad de la información generada. El análisis realizado sugiere que ambas opciones terapéuticas son válidas para el manejo de pacientes con PTI crónica, destacando la importancia de un enfoque colaborativo entre la IA y los hematólogos para maximizar los resultados.

Palabras clave: *Trombocitopenia inmunitaria. Inteligencia artificial. Vida real.*

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Introduction

The concept of intelligent machines capable of assisting humans is over 70 years old. In 1950, Alan Turing wrote his seminal article "Computing Machinery and Intelligence," and in 1956, the term "artificial intelligence" (AI) was coined by Marvin Minsky and John McCarthy. In 2023, with the launch of the ChatGPT (Generative Pre-trained Transformer) application by OpenAI, the concept has become popular. AI is a general concept that encompasses several advanced technologies, such as machine learning, natural language processing, and deep learning, methods that facilitate the extraction of patterns and knowledge from vast amounts of data.

Within AI, ChatGPT is a type of linguistic model based on transformers, capable, among other things, of generating texts similar to those produced by humans, although the model still requires improvement in terms of generating scientific texts[1] and never shows its sources of information. There are publications on the use of ChatGPT in the area of thrombosis and hemostasis, for example, to generate recommendations on thromboprophylaxis in spinal surgery[2] or develop an accurate population pharmacokinetic model for standard half-life factor VIII from literature data[3].

Perplexity AI is another generative AI tool that allows information to be obtained from various sources, and unlike ChatGPT, it shows the sources used to obtain the generated information, enabling their evaluation.

Both tools are very interesting, but they are not stranger to limitations and require a critical evaluation of the information provided. It is not recommended to use these models to generate complete content or replace a proper research process. However, they can be useful for gaining initial knowledge, generating ideas, and conducting complementary research. There are key aspects in any process involving AI, such as the quality of the data with which the system will work or the need for validation and supervision of the results, tasks in which human intervention is crucial[4].

Primary immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura [ITP]) is a disease with an estimated prevalence of 9.5 cases per 100,000 adults and an incidence of 3.3 cases per 100,000 adult-years, which increases with age[5], with no differences between sexes except between the ages of 30 and 60, when it is more prevalent among women[6]. Some authors believe that, given the rapidly accelerating aging of the world's population (from 461 million people older than 65 years in 2004 to about 2 billion in 2050), it is likely that ITP will increasingly become a disease of the elderly[7]. It is often diagnosed in older adults, with a chronic course (60% up to 80%), an insidious onset, or different patterns of clinical expression, and has proven resistant to various treatments (80%)[5,6,8,9]. In patients older than 70, it predominantly affects men and has a higher mortality rates, with a prevalence which is 3-fold greater than in younger adults.

The treatment of ITP has changed considerably in the last 15 years with the arrival, first, of thrombopoietin receptor agonists (the latest of which is avatrombopag)[10], and finally, of a spleen tyrosine kinase inhibitor, fostamatinib[11], capable of reducing the antiplatelet activity of phagocytes. Both are considered first-line therapies in the second line of ITP[12], along with romiplostim and eltrombopag. According to the recommendations of the Spanish ITP Working Group[6] (GEPTI), fostamatinib is especially indicated as the first-line therapy in the second line in patients with high thromboembolic risk, although this is debated even among professionals who developed the guidelines[13]. For other authors[14,15], avatrombopag would not only be the second-line agonist of choice in ITP, but they consider it the optimal second-line therapy in adults, potentially associated with greater efficacy due to its more favorable balance of benefits and acceptability.

Real-world results of the experience in Spain with these 2 therapies have been published: the work by González-López et al.[16] on fostamatinib and that of Pascual et al.[17] on avatrombopag. Both show very good safety and efficacy results, making it difficult to choose one drug over the other. This is where AI, even the most basic generative AI, could be a valuable tool in helping the treatment selection process.

Objective

The objective of this work is to make an indirect comparison in terms of safety and efficacy between fostamatinib and avatrombopag to help select treatment in adult patients with ITP who require a new line of therapy due to the failure of previous ones. We proceed to analyze each study individually and then compare them using generative AI (ChatGPT[4] and Perplexity AI) to try to establish, with the available data, recommendations on which treatment to select.

Results

Fostamatinib, a spleen tyrosine kinase inhibitor, has been approved by the Spanish Agency for Medicines

and Health Products (AEMPS) for the treatment of chronic ITP in adult patients who are refractory to other treatments[11]. The reported response rates are 80% in the second-line therapy and 40% in multi-refractory patients[12], generally early. Real-world results of fostamatinib use in Spanish patients have been reported[16]. This study evaluated its safety and efficacy profile in patients with chronic ITP who had received, at least, 1 previous line of treatment. It included a total of146 patients from 42 Spanish centers, with a median age of 66 years (interquartile range [IQR], 56-80), contrasting with the 53 years (IQR, 20-88) reported in the phase III clinical trial[18]. The median of previous treatments received was 4 (IQR, 2-5), compared to 3 (IQR, 1-13) in the clinical trial[18]. The most common previous treatments were eltrombopag (76.1%), romiplostim (57.2%), IV immunoglobulins (44.2%), and rituximab (29.0%), and 13.8% of patients had previously undergone splenectomy (Table 1).

In terms of efficacy, fostamatinib showed an overall response rate of 79.0%, and a complete response in 53.6% of patients. The median time to response was 11 days (IQR, 7-21). The duration of the response was significant: 83.3% of the time in response during the study period. At 3 months, 80% of patients maintained the response, and at 6 months, the rate remained at 65.7%. These results contrast positively with those reported by the phase III clinical trial[18], which reports a stable response of only 18% and an overall response of 44%, with higher responses in patients whose treatment with thrombopoietin agonists had previously failed. These differences in response rates could be due to less stringent inclusion criteria and the different characteristics of the patients included in both studies. Of note that 83 patients (60.1%) received fostamatinib as monotherapy, achieving a response rate of 85.4%.

Regarding safety, 48.5% of patients experienced adverse effects, generally mild and easily manageable. The most common were diarrhea (20%) and hypertension (15%), which is similar to data from the clinical trial[18]. Serious adverse events, such as deep vein thrombosis and acute myocardial infarction, were reported with an incidence of 0.91 per 100 patients per year. In the clinical trial[18], serious adverse events were reported in 23% of patients, including a transient ischemic attack that resolved spontaneously. A total of 13.8% of patients required bailout therapy during the observation period.

The authors conclude that fostamatinib is an effective treatment for patients with chronic ITP, achieving a rapid response and long-term maintained efficacy. The data show that the real-world study shows a higher overall response rate (79% vs 43%) and complete response rate (53.6% vs 17%) vs the phase III trial. The time to response is also shorter in the real-world study. Although generally well tolerated, adverse effects were observed that require monitoring, but still, fostamatinib is a viable option for patients with ITP who have received various previous treatments.

Avatrombopag has been approved by AEMPS[10] for the treatment of primary chronic ITP in adult patients who do not respond to other treatments. The AVESPA study[17] evaluated the safety and efficacy profile of avatrombopag in the treatment of chronic ITP, including patients who had already received multiple lines of treatment. The sample included a total of 268 patients from 28 Spanish centers, treated from January 2022 through November 2023, with a median age of 59 years (IQR, 42-73). The median number of previous treatments was 3 (IQR, 2-4): 73% had received 2 or more previous lines of treatments and 40% 3 or more. The most common previous treatments were eltrombopag (72%), romiplostim (58%), intravenous immunoglobulins (50%), rituximab (30%), and splenectomy (15%).

In terms of efficacy, avatrombopag achieved an overall response rate of 92%, and a complete response in 82% of the registered patients. Additionally, 65% of patients maintained the response for at least 6 months. The mean time to achieve the initial response is not clearly specified in the study, but more than 90% achieved the response within the first 3 weeks, which is consistent with what was reported in the clinical trial[19], in which 65% of patients showed a partial response by day 8 and up to 85% by day 28. In 65% of patients, no adverse events were reported; the most common were headache (10%), fatigue (8%), and nasopharyngitis (6%), generally mild to moderate. Nine deep vein thromboses were reported, 3 of them associated with thrombocytosis, which constitutes an incidence rate of 2.42 cases per 100 patient-years. This reinforces the idea of adjusting the treatment to the minimum effective dose while maintaining a platelet count between 50 and 150 × 10^3/mL. At the end of the study, a total of 69% of patients were still on avatrombopag, and only 20% required the maximum weekly dose (280 mg); 67% were on < 140 mg per week.

In the phase III clinical trial[19], the most common adverse events reported were headache and fatigue. Although a total of 4 thromboembolic events were reported, 3 of these patients had multiple risk factors for developing them, yet the episodes were independent of platelet count (39 to 271 × 10^3/mL) and the dose

Table 1. Data used by ChatGPT and Perplexity AI for the analyses[16,17]

	Fostamatinib	Avatrombopag
Number of patients/median age, years (IQR)	138/66 (56-80)	268/59 (42-73)
Female sex	55.8%	57.8%
Primary ITP	88.4%	83.8%
Global response rate*	79%	92%
Complete response rate†	53.6%	82%
Time to response, days (IQR)	11 (7-21)	> 90% (max. 21)
Duration of response At 3 months At 6 months	83.3% 80% 65.7%	 65%
Previous treatments, median (IQR)	4 (2-5)	2 (1-3)
Previous treatments	Eltrombopag 76.1% Romiplostim 57.2% IVIG 44.2% Rituximab 29.0% Splenectomy 13.8% 95.1%	CCS 95.1% One or more TPO agonists 59.3% IVIG 49.2% Rituximab 15% Fostamatinib 14.6% Splenectomy 13.1%
Response rate in patients with > 3 previous treatment lines	78.4%	84%
Common adverse effects	48.5% (20% diarrhea, 15% HTN)	35%
Incidence of thrombotic or ischemic events per 100 patient-years	0.91	2.42
Treatment discontinuation	24.8%	15%
Minimum daily dose (package insert)	100 mg/12 h	20 mg/day
Response rate in patients with > 3 previous treatment lines	78.4%	84%

*Avatrombopag > 50,000/mL and fostamatinib > 30,000/mL and, at least, double the initial count with concurrent resolution of bleeding symptoms and absence of any rescue intervention during the previous 8 weeks.
†Avatrombopag > 100,000/mL and fostamatinib > 100,000/mL.
CCS: corticosteroids; HTN: hypertension; IVIG: intravenous immunoglobulin; ITP: primary immune thrombocytopenia; IQR: interquartile range.

used (10 up to 40 mg/day). This highlights that the thromboembolic risk in patients with ITP, whether or not on or thrombopoietin agonists, is multifactorial, as noted in the study conducted by Lambert et al.[20]. A total of 18% of patients required bailout therapy during the observation period (Table 1).

In conclusion, Pascual et al.[17] demonstrate that avatrombopag is an effective drug in patients with chronic ITP, achieving a significant response rate and maintaining long-term efficacy in most cases, which is consistent with what was reported in the phase III trial[19]. Although treatment was well tolerated—there are adverse events that require attention—it remains a viable therapeutic option for patients with ITP, including those who have received multiple previous treatments.

Discussion

As already mentioned, in any process involving AI, a key aspect is the quality of the data entered to generate equally high-quality information. When comparing the two real-life studies, reference is made to the data in table 1, which summarizes the main characteristics of both. Four key aspects are considered:

– The age of the patients: In the fostamatinib study, the median age is 66 years (IQR, 56-80), compared to 59 years (IQR, 42-73) in the AVESPA study, although patients treated with fostamatinib tend to be slightly older.
– The number and type of previous treatment lines: In the AVESPA study, the median is 3 (IQR, 2-4), while for fostamatinib it is 4 (IQR, 2-5), with previous

treatments being fairly similar and comparable, though the fostamatinib group is slightly more treated.
- The number of patients included: This item presents a greater difference, as AVESPA includes a total of 268 patients and the fostamatinib study includes 146 patients.
- The different definition of overall response: For fostamatinib, it is defined as an increase in platelets > 30,000/mL for at least 2 weeks without the need for bailout therapy in the previous 8 weeks, and for avatrombopag, as an increase in platelets > 50,000/mL sustained, thus making the criterion stricter and potentially implying a lower overall response rate vs a lower threshold. It is true that the fostamatinib study includes an additional criterion of not needing rescue treatment in the previous 8 weeks, which is stricter and could decrease the observed response rate. Given that avatrombopag has a higher threshold for defining the response, any direct comparison of response rates should consider these differences to avoid biases. Therefore, ChatGPT-4 adjusts the comparison of efficiency by considering the different response definitions and recalculating response rates, attempting a sensitivity analysis to evaluate how response rates change when applying the criteria of the other study, although this was not possible due to a lack of information. Nonetheless, it states that these differences can significantly affect the assessment of efficiency, because avatrombopag response definition threshold is higher and possibly more demanding. For a more precise comparison, it would be necessary to adjust the response rates considering these definitions or, preferably, conduct additional studies with standardized criteria.

With these results, ChatGPT-4 concludes that the populations in both studies are comparable in terms of age and number of previous treatments, as they have a similar median age and have undergone a similar number of treatment lines before receiving fostamatinib or avatrombopag, suggesting that any differences in the observed safety and efficacy between the 2 drugs are unlikely due to differences in the baseline characteristics of the studied populations.

Regarding sample size, it is suggested that the AVESPA trial[17] is more robust due to the larger number of patients included (268 vs 146), so the results for avatrombopag may be more generalizable. On the other hand, that larger number of patients can also imply greater variability in response to avatrombopag and provide a more complete picture of its safety and efficacy in a more diverse population.

As for thrombotic risk, a common method to compare incidences between two groups is the chi-square test or a proportions test. ChatGPT-4, to determine if the difference between 0.91 and 2.42 cases per 100 patient-years is statistically significant, first opts for an initial approach with the Z-test for 2 proportions (Annex 1, supplementary data), concluding that the observed difference between the 2 studies is not statistically significant. Then it performs the comparison with the chi-square test and reaches the same conclusion: there is no statistically significant difference in the incidence of thrombotic or ischemic events between the two studies.

Probably the most challenging part of the analysis is the assessment of efficiency, partly due to the available data from both studies, which are incomplete or absent regarding the doses used. Even so, to perform this analysis, ChatGPT-4 uses the relevant data referred to in table 1. According to its efficiency analysis, if only two items (safety and efficacy) are considered, both drugs can be considered equally efficient in terms of overall and complete response. However, avatrombopag seems safer, with a lower incidence of common, mild-to-moderate adverse effects vs fostamatinib. Considering safety and efficacy, avatrombopag could be the preferred treatment due to its more favorable safety profile, although both are highly effective.

When calculating efficiency also considering financial cost, the analysis presents the same limitation, that is, absence of data or incomplete data on the doses used, especially in the AVESPA study. The prices used for the analysis correspond to the free sale price from the Ministry of Health (Table 2). The doses considered for the calculation come from the scant information reported in real-life studies.

For fostamatinib, the recommended initial dose is 100 mg twice a day; initial dose in 107 patients. After 4 weeks, it can be up titrated to 150 mg twice a day depending on platelet count and tolerability; 85 patients increased the daily dose to the maximum of 300 mg, and 31 patients started treatment directly with that maximum dose due to their extreme refractoriness to previous treatments. The median time from the start of fostamatinib to dose titration to 150 mg twice a day was 28 days (IQR, 16-39 days). The median duration of treatment for the entire cohort was 207 days (IQR, 78-449 days). However, in patients who did not respond, the duration was 48 days (IQR, 28-70 days).

For avatrombopag, the initial dose is assumed to be 20 mg/day in 100% of patients, as indicated in its technical data sheet[10]. At the end of the follow-up period, from January 2022 through November 2023, 67% of

Table 2. Treatment cost

	Fostamatinib	Avatrombopag
Box of 60 tablets of 100 mg	€3100 €51.66/per tablet €103.33/per day	
Box of 60 tablets of 150 mg	€4650 €77.50/per tablet €155/per day	
Box of 10 tablets of 20 mg		€925 €92.5/per tablet €92.5/per day
Box of 15 tablets of 20 mg		€1390 €92.66/per tablet €92.66/per day

Source: https://www.farmaceuticos.com/botplus/.

patients needed avatrombopag at doses ≤ 140 mg/week and 20% at doses of 280 mg/week. Therefore, it is unknown if 100% of patients started treatment with the recommended dose in the technical data sheet, the timing of the first adjustment, and the percentage of patients who required dose adjustment.

To perform a global efficiency evaluation of treatments, considering overall and complete response rates, adverse events, the need for bailout therapy, and financial cost, it uses a weighted approach normalizing the data to a common scale (e.g., 0 up to 1), where a higher value indicates better performance. In this way, an overall efficiency score of 0.71565 is obtained for fostamatinib and 1 for avatrombopag. Since avatrombopag has a higher overall score due to its greater efficacy and lower incidence of adverse events, it is more efficient in terms of cost per day of overall response in the minimum cost scenario. If financial cost is a critical factor, avatrombopag could be the preferred option. If clinical efficacy and reduction of adverse events are more of a priority, again avatrombopag could be the best choice, and this could have an impact in a resource-limited setting.

In an economically precarious situation, avatrombopag is more efficient in terms of cost per day of overall response than fostamatinib, at least in the minimum cost scenario. It would be preferable due to its lower cost per day of effective response (€100.54 vs €130.85 for fostamatinib). The lower treatment costs make it a more accessible option for patients and healthcare systems with limited resources (Annex 2, supplementary data) All in all, it warns that the formula used is a simplified way of combining costs and effectiveness, and a more detailed analysis could consider more factors, such as costs of adverse events, quality of life, and other long-term effectiveness aspects.

Perplexity AI, when comparing the efficiency of both treatments using the same data (Table 1), concludes that:

– In terms of cost: Avatrombopag remains the most cost-effective treatment in terms of cost per day of overall response, despite fostamatinib having a good response rate.
– In terms of efficacy: Fostamatinib has a lower stable response rate vs avatrombopag, but its use may be more effective in refractory patients.

Perplexity AI understands, like ChatGPT-4, that avatrombopag is more efficient, but it is essential to consider the clinical context and individual patient characteristics when evaluating the efficiency of any treatment. Perplexity AI agrees that avatrombopag can be seen as more efficient due to its higher response rate and safety profile. However, it warns that different analyses and assumptions can lead to different conclusions, especially if long-term factors such as treatment duration and the need for dose titration are considered. Thus, it concludes that:

– The need to increase the dose of fostamatinib to 150 mg twice a day for many patients increases costs (maximum cost per day of overall response: €196.20). The long-term effective dose assumed for avatrombopag suggests that many patients can maintain lower doses, which obviously reduces costs (Annex 2, supplementary data).
– Drug prices may vary across different autonomous communities and hospitals within the same community, and evaluations may differ depending on local costs.
– Costs associated with managing side effects and the need for rescue treatment should be considered, which will affect the overall cost assessment.

Finally, we proceeded to make a critical comparison between the conclusions made by both AI tools, from the point of view of Chat GPT-4 and from the point of view of Perplexity AI (Tables 3 and 4).

Obviously, this comparison exercise has numerous limitations: starting from observational studies, there may be discrepancies in the clinical practice followed. The concurrent use of other drugs and disease severity affect the results. The measurement of outcomes (overall response rates) and the follow-up period are different. The percentage of patients requiring bailout therapy (or which type) is not clearly defined (assumed to be 13.8% for fostamatinib and 18% for avatrombopag), and

Table 3. ChatGPT-4o: critical analysis of differences and recommendations between ChatGPT-4o and Perplexity AI

Aspect	ChatGPT-4o	Perplexity AI
Clinical efficiency	Avatrombopag is clinically more efficient due to higher global and complete response rates and fewer adverse events.	Fostamatinib, while reducing the need for rescue treatment, has a higher incidence of adverse events. Both are effective, but Avatrombopag stands out with a higher response rate. Fostamatinib might be more effective in refractory patients. Emphasizes the importance of safety in decision-making.
Treatment cost	Fostamatinib could be more costly in the short to medium term.	Avatrombopag may be more cost-effective in the long term, especially in the Spanish context, making it a more viable option compared to Fostamatinib.
General recommendations	Patients with a limited budget: recommends avatrombopag due to lower initial cost, with careful monitoring of adverse events. Prioritize clinical efficiency: recommends avatrombopag for its better response rates and lower incidence of mild to moderate adverse events. Long-term considerations: proposes a detailed cost analysis including management of adverse events and treatment duration. Individualization of treatment: emphasizes the need to consider each patient's individual profile, including prior responses and comorbidities.	Individual patient profile: critical to choose treatment based on specific patient characteristics, including severity of thrombocytopenia and comorbidities. Safety and efficacy: assess safety and efficacy profile, considering avatrombopag for higher response rates and fostamatinib for refractory patients. Cost and accessibility: avatrombopag may be more cost-effective in the long term, especially in the Spanish context. Close monitoring: recommends close monitoring of platelet counts and adverse events. Combination with other treatments: considers the possibility of combining fostamatinib or avatrombopag with other drugs to enhance efficacy and reduce dosage.
Final considerations	Although recommendations align with clinical guidelines and lack bias, it cannot replace human clinical judgment. Highlights the importance of traditional clinical studies to validate treatments and ensure personalized care.	Both are valid options, and a multidisciplinary approach involving the patient, hematologist, and primary care team is recommended to optimize therapeutic outcomes.

Table 4. Perplexity AI: critical analysis of differences and recommendations between ChatGPT-4o and Perplexity AI

	ChatGPT-4o	Perplexity AI
Clinical efficiency	Avatrombopag has higher overall and complete response rates and a lower incidence of adverse events compared to fostamatinib. Fostamatinib appears to show a lower need for bailout therapy but a higher incidence of adverse effects.	Both are effective, but emphasizes that avatrombopag might be more cost-effective in the long term. Suggests that fostamatinib might be more effective in refractory patients, introducing an important variable in the discussion of clinical efficacy.
Treatment cost	Fostamatinib is more expensive per patient; moreover, in the long term, it might be even more costly due to the management of adverse events and the need for additional treatments.	Avatrombopag may be more cost-effective in the long term, especially in our setting. Fostamatinib shows discrepancies between the efficacy reported in clinical trials and in clinical practice; this is crucial for evaluating cost-effectiveness.
Treatment recommendations	Avatrombopag is recommended for patients where efficacy and safety are priorities.	Proposes a more individualized approach; suggests that the choice should be based on specific patient characteristics, severity of thrombocytopenia, and response to previous treatments. Suggests considering combination treatments to improve efficacy.
Multidisciplinary approach	Emphasizes the importance of human clinical judgment and the need for traditional clinical studies to validate treatments.	Reinforces the need for a multidisciplinary approach involving the patient and the medical care team to optimize therapeutic outcomes.

in general, the statistical analysis performed is simplified and lacks adequate adjustments. Although the simplified analysis can provide a global view of the efficiency of both drugs, we must consider the mentioned limitations for an adequate interpretation of results. Although this analysis could be indicative for choosing between one drug or the other, considering the patient's individual characteristics, it can never replace the proper clinical judgment on which our decisions must be based.

Conclusions

AI is here to stay, and its role in the development of medicine, at all levels, will be crucial in the future. AI tools can transform medicine by optimizing decision-making, accelerating research, and improving patient follow-up. ChatGPT-4 and Perplexity AI can help make recommendations based on scientific literature and previous study data, thus contributing to the financial sustainability of the National Health System, among other aspects. The use of this basic generative AI (ChatGPT-4o and Perplexity) is already a reality, and in the analysis of these treatments for PTI in real life, it could be a valuable instrument for comparing the safety and efficacy of different therapeutic options. Both tools agree on the importance of individualizing treatment and considering both the safety and efficacy of the drugs. They also align in their financial cost recommendations, suggesting an initial economic advantage for avatrombopag, especially in Spain. Perplexity AI offers a more nuanced analysis focused on individualizing treatment, while ChatGPT-4 focuses more on general recommendations based on costs and efficacy. This contrast suggests that, although both tools can provide valuable information, a comprehensive clinical evaluation adapted to the specific needs of each patient is necessary, requiring a collaborative approach between AI and hematologists to maximize results.

We should not forget that AI still has limitations: ensuring the quality of the provided data is crucial (in this case, insufficient or even absent for some key aspects of the analysis); proper validation of the results through human supervision of the entire process is essential to ensure the quality of the generated information. Additionally, in this specific case, as already mentioned, the formulation of hypotheses by the operator can generate biases in the responses, and even different operators could sometimes generate discordant responses.

Real-life study results, beyond the analysis performed by AI tools, show that both drugs, avatrombopag and fostamatinib, are effective in managing chronic ITP, showing good response rates and response duration, with an adequate tolerability and safety profile. The choice of one drug or the other may depend on additional clinical factors, patient preferences (when the professional has all options at hand), the hematologist's experience, and financial aspects. Both options are valid for managing patients with chronic ITP refractory to multiple previous treatments, with very good global and complete response rates. The selection of treatment should be individualized and personalized, considering all the described factors.

Supplementary data

Supplementary data are available at DOI: 10.24875/RHT.M24000014. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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References

1. Klang E, Levy-Mendelovich S. Evaluation of OpenAI's large language model as a new tool forwriting papers in the field of thrombosis and hemostasis. J Thromb Haemost. 2023;21:1055-8.

2. Duey AH, Nietsch KS, Zaidat B, Ren R, Ndjonko LCM, Shrestha N, et al. Thromboembolic prophylaxis in spine surgery: an analysis of ChatGPT recommendations. Spine J. 2023;23:1684-91.
3. Cloesmeijer ME, Janssen A, Koopman SF, Cnossen MH, Mathôt RAA; SYMPHONY consortium. ¿ChatGPT in pharmacometrics? Potential opportunities and limitations. Br J Clin Pharmacol. 2024;90:360-5.
4. Rashidi H, Bowers K, Reyes Gil M. Machine learning in the coagulation and hemostasis arena: an overview and evaluation of methods, review of literature, and future directions. J Thromb Haemost. 2023;21:728-43.
5. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: a critical review of published reports. Am J Hematol. 2010;85:174-80.
6. Schoonen WM, Kucera G, Coalson J, Li L, Rutstein M, Mowat F, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. Br J Haematol. 2009;145:235-44.
7. Palandri F, Santoro C, Carpenedo M, Cantoni S, Barcellini W, Carli G, et al Management of elderly patients with immune thrombocytopenia: real-world evidence from 451 patients older than 60 years. Thromb Res. 2020;185:88-95.
8. Abrahamson PE, Hall SA, Feudjo-Tepie M, Mitrani-GoldFS, Logie J. The incidence of idiopathic thrombocytopenicpurpura among adults: a population based study andliterature review. Eur J Haematol. 2009;83:83-9.
9. Yong M, Schoonen WM, Li L, Kanas G, Coalson J, Mowat F, et al. Epidemiology of paediatric immune thrombocytopenia in the General Practice Research Database. Br J Haematol 2010;149:855-64.
10. Avatrombopag. Ficha técnica. AEMPS. (Consultado el 06-07-2024.) Disponible en: https://cima.aemps.es/cima/dochtml/ft/1191373/FT_1191373.html.
11. Fostamatinib. Ficha técnica. AEMPS. (Consultado el 07-07-2024.) Disponible en: https://cima.aemps.es/cima/dochtml/ft/1191405002/FT_1191405002.html.
12. Mingot-Castellano ME, Canaro Hirnyk M, Sánchez-González B, Álvarez-Román MT, Bárez-García A, Bernardo-Gutiérrez A, et al. Recommendations for the clinical approach to immune thrombocytopenia: Spanish ITP Working Group (GEPTI). J Clin Med. 2023;12:6422.
13. Sociedad Española de Hematología y Hemoterapia. Recomendaciones PTI. Consenso Delphi. Evaluación de la práctica clínica habitual en España ante la llegada de nuevos fármacos para el tratamiento de la PTI. Disponible en: file:///C:/Users/ccomp/Downloads/Slide-Kit-Resultados-Consenso-Delphi-PTI.pdf.
14. Liu Y, Zhang HX, Su J, Geng QC, Lin X, Feng CX. Efficacy and incidence of treatment related adverse events of thrombopoietin receptor agonists in adults with immune thrombocytopenia: a systematic review and network meta-analysis of randomized controlled study. Acta Haematol. 2023;146:173-84.
15. Deng J, Hu H, Huang F, Huang C, Huang Q, Wang L, et al. Comparative efficacy and safety of thrombopoietin receptor agonists in adults with thrombocytopenia: a systematic review and network metaanalysis of randomized controlled trial. Front Pharmacol. 2021;12:704093.
16. González-López TJ, Bermejo N, Cardesa-Cabrera R, Martínez V, Aguilar-Monserrate G, Pérez Segura G, et al. Fostamatinib effectiveness and safety for immune thrombocytopenia in clinical practice. Blood 2024 Jun 6:blood.2024024250. doi: 10.1182/blood.2024024250. Online ahead of print.
17. Pascual Izquierdo C, Sánchez B, Canaro Hirnyk M, García-Donas G, Menor Gómez M, Monsalvo Saornil S, et al Avatrombopag in ITP. A real-world study of the Spanish ITP Group (GEPTI). EHA 2024; abstr. P2240. Disponible en: https://library.ehaweb.org/eha/2024/eha2024congress/420327/cristina.pascual.izquierdo.avatrombopag.in.immune.thrombocytopenia.28pti29.a.html?f=menu%3D6%2Abrowseby%3D8%2Asortby%3D2%2Ace_id%3D2552%2Aot_id%3D29183%2Amarker%3D5100%2Afeatured%3D18527.
18. Bussel JB, Arnold DM, Boxer MA, Cooper N, Mayer J, Zayed H, et al, Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program. Am J Hematol. 2019;94:5 46-53.
19. Jurczak W, Chojnowski K, Mayer J, Krawczyk K, Jamieson BD, Tian W, et al. Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol. 2018;183:479-90.
20. Lambert C, Maitland H, Ghanima W. Risk-based and individualised management of bleeding and thrombotic events in adults with primary immune thrombocytopenia (ITP). Eur J Haematol. 2024;112:504-15.

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CASE REPORT

Antiphospholipid syndrome: is there a preclinical period?

Síndrome antifosfolipídico: ¿existe un periodo preclínico?

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial, venous, or microvascular thrombosis, obstetric morbidity, and various non-thrombotic manifestations in patients with persistently positive antiphospholipid (APL) antibodies[1,2]. The prevalence of APS is estimated at 50 per 100,000 people and is 5 times more common in women vs men[1]. Catastrophic APS is a severe, acute manifestation, accounting for 1% of cases, characterized by microthrombosis in multiple areas, leading to multiple organ dysfunction, with high mortality rates (29% up to 75%)[3].

In the absence of diagnostic criteria for APS, clinicians have used "classification" criteria: initially the Sapporo criteria (1999 and revised in 2006)[4,5], and more recently, those of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) (2023)[2], aiming to include a heterogeneous group of patients, primarily for research rather than for confirmation diagnoses, guiding therapy, or monitoring. Some cases do not meet the classification criteria for APS, yet present diagnostic and therapeutic challenges in clinical practice[6,7] This is the case for asymptomatic patients with persistently positive APL antibodies. It is known that these antibodies can also be positive in conditions unrelated to APS (e.g., elderly individuals, neoplastic diseases, pregnancy), reflecting their low specificity[1,8]. Additionally, the contribution of each APL antibody type to thrombotic risk varies and may be additive in certain cases[2]. Therefore, the thrombotic event risk in this clinically asymptomatic patient group represents uncertainty for clinicians.

We present an APS case that illustrates the progression from an asymptomatic or preclinical stage, with positive APL antibodies and mild thrombocytopenia, to a catastrophic clinical onset.

Case report

A 55-year-old woman with a past medical history of chronic idiopathic urticaria under follow-up and treatment with the allergy service. A routine blood test revealed confirmed mild thrombocytopenia (128 x 10^3 μL [reference values: 150-450]) with no abnormalities in the peripheral blood smear. Further testing showed triple positivity for APL antibodies at high titers measured by ELISA: anti-β_2-glycoprotein I (anti-β_2GPI) IgG 188 U/mL (reference values: 20-40), anticardiolipin (aCL) IgG 168 GPL (reference values: 20-40), lupus anticoagulant (LA) positive (screened with dRVVT and silica-activated APTT), with positive mixing and confirmatory studies.

A second determination after 12 weeks remained positive.

Prophylactic treatment with acetylsalicylic acid (ASA) was started, and periodic follow-up at the coagulation clinic showed persistent laboratory abnormalities

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(high APL antibody titers > 80 U/mL and mild thrombocytopenia) with no clinical signs consistent with APS or systemic autoimmune disease.

Five years after detecting these laboratory abnormalities, the patient presented to the ER with cyanosis in the first toe of the right foot, evolving over a few hours, along with fever, diffuse abdominal pain, and postprandial vomiting. Blood tests showed mild thrombocytopenia (100 x 10^3 μL), no other cytopenias, no peripheral blood smear abnormalities, and no renal or hepatic dysfunction. Imaging modalities (Doppler ultrasound and angiography) revealed renal and splenic infarcts, as well as thrombosis in the infrarenal abdominal aorta and various portions of the right popliteal artery. No adenopathy, visceromegaly, or lesions suggestive of solid neoplasm were found, and serial blood cultures tested negative. Autoimmune tests were repeated, showing positive APL antibodies only. Anticoagulant treatment with low-molecular-weight heparin (LMWH) (enoxaparin 60 mg subcutaneously every 12 hours) was started, a mechanical thrombectomy was performed, and a transpopliteal revascularization of the distal trunks was attempted with partial success and without further clinical progression of tissue ischemia. No clear trigger or additional cardiovascular or thrombotic risk factor was identified in the medical history.

Given the previous laboratory findings, a diagnosis of probably primary catastrophic APS was established. Treatment was initiated with high-dose corticosteroids (methylprednisolone 500 mg IV/day for 3 days), hydroxychloroquine (200 mg/day orally), immunoglobulins (0.4 g/kg/day IV for 5 days), anti-CD20 monoclonal antibody (375 mg/m^2 IV in a single dose), and plasmapheresis (5 sessions), achieving a favorable outcome. Subsequently, outpatient follow-up continued with a tapering dose of oral corticosteroids, hydroxychloroquine, ASA, and acenocoumarol to maintain an international normalized ratio (INR) between 2 and 3. Since there was no adequate correlation between capillary (POC device: CoaguChek XS) and venous blood INR measurements (Quick method), it was decided to continue measurement by the Quick method, maintaining a therapeutic range without bleeding complications or new thrombotic events.

Discussion

Patients with positive APL antibodies without defining clinical events of APS (preclinical stage) have an annual thrombotic risk between 1% and 5% in an apparently healthy population, being higher in patients with systemic lupus erythematosus[9]. Despite the difficulty in predicting thrombotic events in these patients, laboratory variables have been used as potential markers. Traditionally, high-risk cases have been defined as "triple positive," meaning positivity for all 3 antibodies (LA, aCL, and anti-β_2GPI); cases with persistently positive LA; "double positives" (aCL and anti-β_2GPI); and/or high titers of APL antibodies[8,10]. For these high-risk cases, some experts recommend low-dose ASA (75-100 mg/day) as primary prophylaxis; however, in a prospective study, "triple positive" patients had an annual thromboembolic risk of 5%, which did not decrease with ASA use[11]. A randomized clinical trial (APSALA) that sought to answer this question (ASA in primary prophylaxis) was stopped early due to the low rate of thrombosis, without detecting a reduction in thrombotic events[12].

Besides ASA, LMWH is often recommended in high-risk situations, albeit with a low level of evidence[8,10]. Even so, the actual time window to clinical presentation remains an enigma. These antibodies do not, *per se*, cause thrombotic complications in healthy subjects, but they may act as a "first hit" that varies depending on genetic, ethnic, and geographic factors, given the variable distribution of APS in epidemiological studies[8]. According to the "second hit" hypothesis, certain factors can trigger the thrombotic process by acting as biological stressors (e.g., viral infections [hepatitis B, C, human immunodeficiency virus, severe acute respiratory syndrome coronavirus[2] or bacterial infections [Coxiella burnetii]), eventually leading to APS development[8].

In clinical practice, patients with a positive APL antibody profile but no APS classification criteria should be periodically evaluated for not only thrombotic signs (microvascular, cardiac, obstetric) but also for the dynamic risk of thrombotic events (concomitant systemic autoimmune diseases, as well as cardiovascular and venous thromboembolic disease risk factors)[2] to establish preventive measures and attempt to mitigate the risk of modifiable factors. However, these measures may be insufficient in some cases, and prospective and comparative studies are necessary to determine which early interventions may be beneficial.

In terms of catastrophic APS, most cases are primary and develop within the first 5 years of follow-up after APS diagnosis; in about half of cases, it is the initial sign[3]. However, as this is an extremely rare condition, few studies elucidate the true prevalence, incidence, and time window from APL antibody detection. The latest CAPS registry data shows that peripheral arterial involvement, as in our case, is present in only 37% of cases, and renal infarcts in 8.7%[13]. The most common

clinical signs are renal, pulmonary, and peripheral venous system involvement[13]. Despite high mortality, data from this registry show that 66% of cases are symptom-free under anticoagulant therapy at the 67-month follow-up[14]. Catastrophic APS should be suspected in cases presenting with this type of severe multisystemic involvement over a short period, to address both potential triggers and the inflammatory and thrombotic storm.

Currently, vitamin K antagonists are the anticoagulants of choice for secondary prophylaxis[10]. INR measurement is typically done using the prothrombin time with the Quick method on venous blood[15,16]. However, given the frequent INR monitoring required in these cases, many patients are monitored with point-of-care (POC) devices, usually obtaining good correlations for INR between 1.5 and 4.5[16]. Nonetheless, false INR elevations can occur due to APL interference (mainly with LA and anti-β_2GPI) with reagents (recombinant thromboplastin times) in POC devices[15,16]. This may lead to inadequate anticoagulant dosing, with associated risks. A practical approach may be to restrict POC use to APS patients with sustained agreement between digital and venous INR of < 0.5, regardless of LA positivity[15]. If there is no concordance, it is preferable to continue INR measurement with venous blood, ideally with the Owren method (less sensitive to interference)[16]. Other methods may be useful; however, a therapeutic range has not been systematically established for methods like chromogenic factor X, anti-Xa activity, chromogenic ecarin-based assays, and thrombin generation[15].

Conclusions

There is no standardization for clinical follow-up of patients with positive APL antibodies without APS clinical signs. Despite recommended prophylactic measures for high-risk positive APL antibody cases in preclinical stages, these may still present with catastrophic manifestations of the disease. APL interference can lead to INR discrepancies (capillary vs venous) and thus inadequate control of anticoagulant therapy with vitamin K antagonists in these cases.

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Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have indeed used generative artificial intelligence, specifically ChatGPT-4, for the efficiency analysis of the 3 treatments, through the analysis of the results reported in the different studies.

References

1. Dabit JY, Valenzuela-Almada MO, Vallejo-Ramos S, Duarte-García A. Epidemiology of antiphospholipid syndrome in the general population. Curr Rheumatol Rep. 2022;23(12):85.
2. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, A et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol. 2023;75(10):1687-702.
3. Rodriguez-Pintó I, Espinosa G, Cervera R. What we know and what we don't know about catastrophic antiphospholipid syndrome. Rheumatology (Oxford). 2024;63(SI):SI46-SI53.
4. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999;42(7):1309-11.
5. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.
6. Cecchi I, Radin M, Foddai SG, Arbrile M, Barinotti A, Rubini E, et al. "How we treat" clinical dilemmas in antiphospholipid syndrome: A case-based approach. Eur J Intern Med. 2023;107:1-6.
7. Crowther M, Erkan D. A new approach to antiphospholipid antibody syndrome. Res Pract Thromb Haemost. 2023;7(7):102226.
8. Grygiel-Górniak B, Mazurkiewicz Ł. Positive antiphospholipid antibodies: observation or treatment? J Thromb Thrombolysis. 2023;56(2):301-14.
9. Zuo Y, Barbhaiya M, Erkan D. Primary thrombosis prophylaxis in persistently antiphospholipid antibody-positive individuals: where do we stand in 2018?. Curr Rheumatol Rep. 2018;20(11):66.
10. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019;78(10):1296-304.
11. Pengo V, Ruffatti A, Legnani C, Testa S, Fierro T, Marongiu F, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood. 2011;118(17):4714-8.
12. Erkan D, Harrison MJ, Levy R, Peterson M, Petri M, Sammaritano L, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. Arthritis Rheum. 2007;56(7):2382-91.
13. Rodríguez-Pintó I, Moitinho M, Santacreu I, Shoenfeld Y, Erkan D, Espinosa G, et al. Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev. 2016;15(12):1120-4.
14. Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, et al. Long term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis. 2003;62(6):530-3.
15. Cohen H, Efthymiou M, Devreese KMJ. Monitoring of anticoagulation in thrombotic antiphospholipid syndrome. J Thromb Haemost. 2021;19(4):892-908.
16. Noordermeer T, Urbanus RT, Wong CY, Jansma JJ, Wiersma NM, Zivkovic M, et al. Interference in point-of-care international normalized ratio monitoring in patients with lupus anticoagulant is correlated with anti-β2-glycoprotein I antibody titers. Res Pract Thromb Haemost. 2022;7(1):100011.

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SELECTED IMAGE

In vitro culture of megakaryocytes forming proplatelets from CD34+ cells obtained from peripheral blood

Cultivo in vitro de megacariocitos formando proplaquetas a partir de células CD34+ obtenidas de sangre periférica por inmunoselección positiva

*Ana Zamora-Canovas, Ana Marín-Quílez, Pedro L. Gómez-González, Ana Sánchez-Fuentes, Patricia Guerrero-Serrano, M.ª Luisa Lozano-Almela, and José Rivera**

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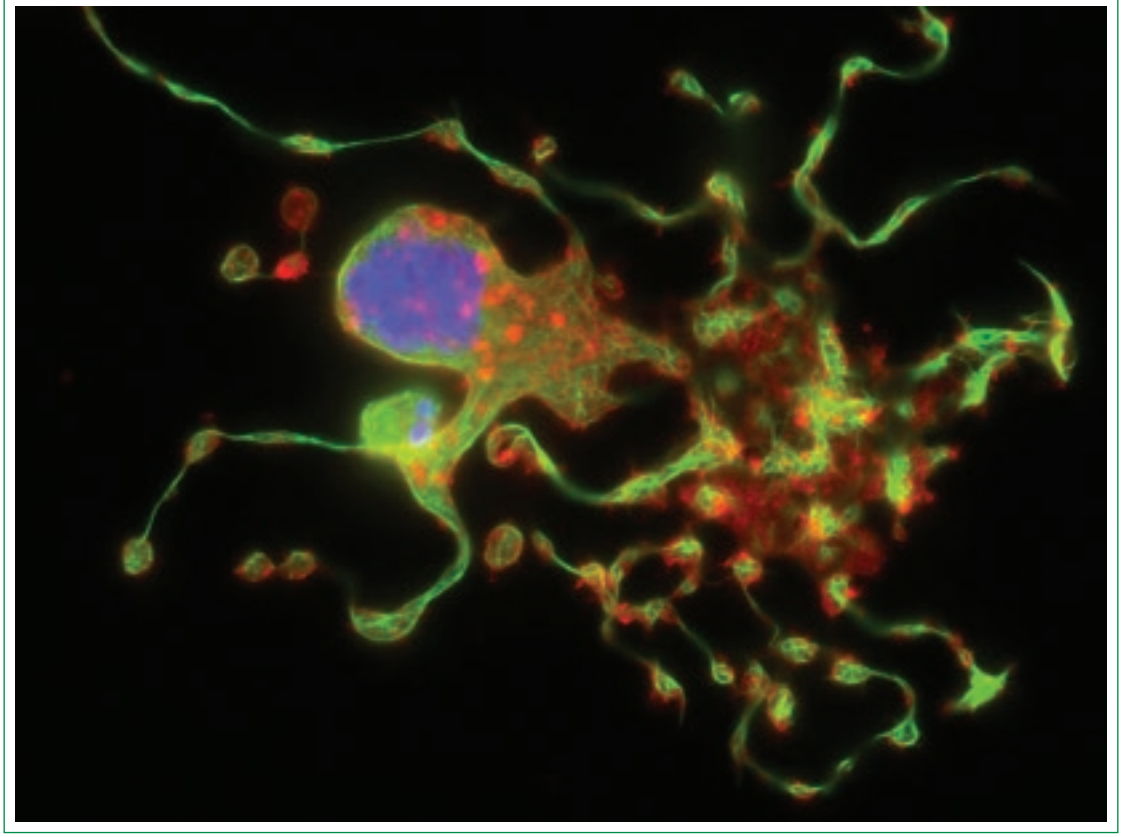
The culture is stained for F-actin (green), tubulin (red), and DAPI (blue).



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