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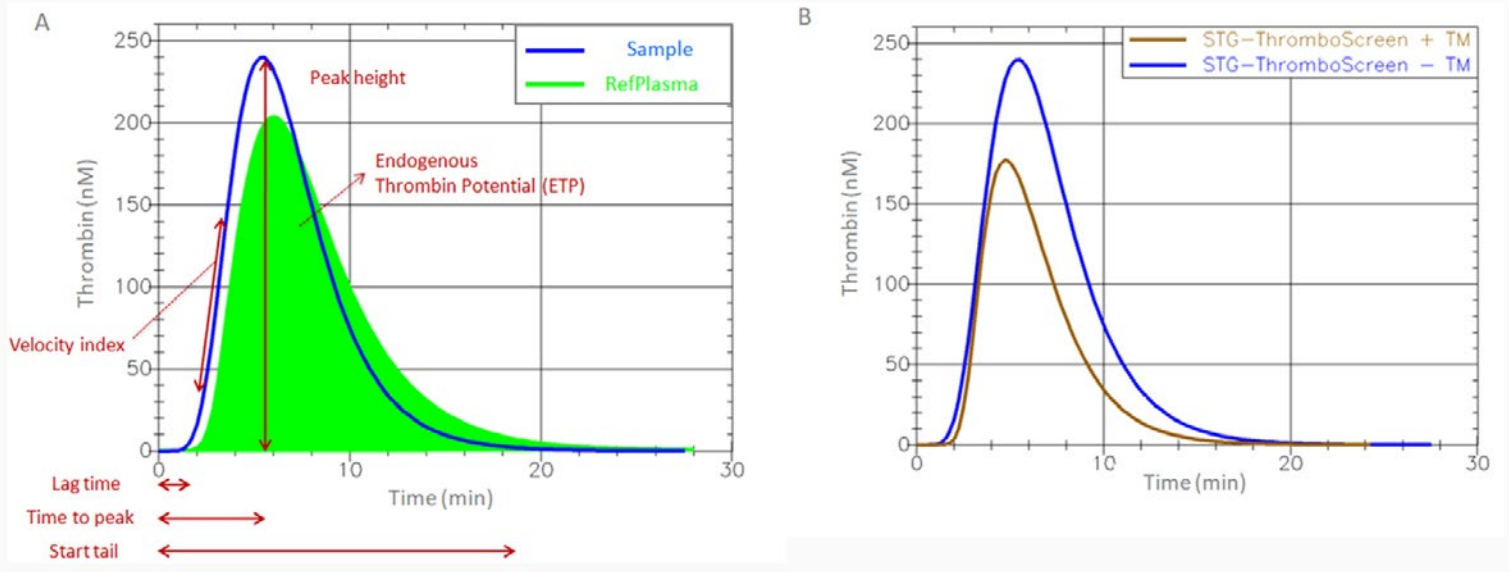

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EDITORIAL

Editorial

Editorial

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The study of hemostasis and thrombosis is currently in a phase where, as in all of medicine and life sciences, therapeutic and technological innovation is accelerating. The scientific journal *Haemostasis and Thrombosis – Ibero-American Journal of Thrombosis and Haemostasis* aims to contribute to creating its own space for updated dissemination of this new knowledge, also filling gaps, such as linguistic ones, that other journals do not cover, while striving to be accessible to all interested professionals through its Open Access nature and no publication costs. With this approach, the journal aspires to be a platform for sharing experiences, both in major referral centers and in peripheral hospitals. This concept has guided the preparation of the present fourth issue of 2025.

Hemophilia remains central to much of the current therapeutic innovation in hemostasis. In this issue, the review article on efanesoctocog alfa raises the question of whether we are facing a new standard in hemophilia A prophylaxis. Efanesoctocog alfa, an ultra-long half-life recombinant factor VIII concentrate, breaks through the ceiling historically imposed on the half-life of these FVIII factor drugs. The review introduces the idea of returning to "physiological" prophylaxis based on factor VIII with a radically lower treatment burden than before, and presents it within the context of the development of non-replacement therapies. Meanwhile, the case report of the first patient with severe hemophilia B treated with hemodialysis in Uruguay highlights the evolution of care needed by patients with coagulopathies, who, as they improve their life expectancy, begin to accumulate "common" comorbidities of aging, including chronic kidney disease. The study demonstrates that hemodialysis can be performed safely in these patients if it is well-planned.

Regarding clinical practice in the field of thrombosis, the article on cardiovascular risk assessment in patients with primary immune thrombocytopenia reminds us that "thrombocytopenia" is not synonymous with "low thrombotic risk." In a cohort of 55 elderly patients, with the use of thrombopoietin receptor agonists and a significant burden of cardiovascular risk factors such as hypertension or dyslipidemia, the article underscores the need for a comprehensive approach that is not limited to achieving "safe" platelet counts, but also incorporates a systematic evaluation of cardiovascular risk factors. A relevant aspect of this study is the declared use of generative artificial intelligence (AI) to support the design and execution of the statistical analysis. This demonstrates how AI is beginning to enter scientific work, which opens opportunities but also requires extreme methodological transparency to establish appropriate boundaries. The challenge is not so much using AI as using it well: with transparency, external validation, and never relinquishing clinical judgment.

Regarding the hemostasis laboratory, this issue includes a review on a global coagulation assay: the thrombin generation assay. Global assays provide a

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much closer view of the real behavior of the hemostatic system than classical tests. Their progressive standardization and automation bring them closer to routine laboratory practice, and thanks to this, the thrombin generation assay is consolidating as the most promising global assay for integrating the balance between procoagulant and anticoagulant factors. The review, conducted by the working group of the Spanish Society of Thrombosis and Hemostasis dedicated to this test, comprehensively examines the technical evolution and current state of its automation. Standardization, the use of reference plasmas, automation, and the International Society on Thrombosis and Haemostasis (ISTH) recommendations for controlling preanalytical and analytical factors now allow for the incorporation of this test into the daily work of clinical coagulation laboratories.

Finally, we want to especially highlight the letter from the Cooperative Latin American Group on Hemostasis and Thrombosis (CLAHT) celebrating its first 50 years. From the first cooperative conferences in Havana in 1973 to the present, with experts from 16 countries and around 400 members, CLAHT has demonstrated that only through cooperation can robust registries, clinical guidelines adapted to the reality of each healthcare system, and training programs that reach beyond large referral centers be developed. New treatments and technologies are being incorporated unevenly, depending on the country and hospital, mainly for economic reasons. In this environment of unequal access, the voice of scientific cooperation networks such as CLAHT is important in the pursuit of equity in medicine.

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GUIDES AND CONSENSUS

Fully automated thrombin generation assays: current characteristics, advances, and clinical relevance

Ensayos automatizados de generación de trombina: características actuales, avances y relevancia clínica

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Abstract

The thrombin generation assay (TGA) is a diagnostic tool that enables a global assessment of hemostasis. In recent years, technical advances have been made to achieve full automation of these assays, with the aim of ensuring standardization and consistency across studies. Currently, two fully automated devices are available: ST-Genesia® (Diagnostica Stago, Asnières-sur-Seine, France) and Ceveron® alpha TGA (Technoclone, Vienna, Austria). This is a highly versatile tool that has demonstrated clinical applicability both in the field of bleeding disorders – by assessing patients' bleeding phenotypes and monitoring their hemostatic treatment – and in thrombotic disorders, as it can identify thrombotic risk profiles not only for venous thrombosis but also for cardiovascular risk and cancer-associated thrombosis. Its role is also being investigated in the monitoring of anticoagulant therapy and the hemostatic status of patients with liver cirrhosis.

Keywords: *Thrombin generation assay. Global assay. Automatization.*

Resumen

El test de generación de trombina es una herramienta diagnóstica que permite evaluar de forma global la hemostasia. En los últimos años se ha avanzado técnicamente para lograr automatizar completamente dichos estudios con el fin de lograr su estandarización y homogeneidad. En la actualidad están disponibles dos dispositivos, ST-Genesia® (Diagnostica Stago, Asnières-sur-Seine, France) y Ceveron® alpha TGA (Technoclone, Vienna, Austria) completamente automatizados. Se trata de una herramienta muy versátil que ha demostrado su aplicabilidad clínica tanto en el campo de la diátesis hemorrágica evaluando el fenotipo hemorrágico de los pacientes y la monitorización del tratamiento hemostático, como en el campo de la diátesis trombótica siendo capaz de identificar el perfil de riesgo trombótico no solo en trombosis venosa sino también en riesgo cardiovascular y trombosis asociada a cáncer. También se está evaluando su papel en la monitorización del tratamiento anticoagulante y el estado hemostático de pacientes con cirrosis hepática.

Palabras clave: *Test de generación de trombina. Test global. Automatización.*

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Introduction

The thrombin generation assay (TGA) is an advanced diagnostic tool designed to evaluate the entire coagulation process, particularly focusing on the thrombin generation (TG) phase. Thrombin, a critical enzyme in the coagulation cascade, plays a pivotal role in blood clot formation. TGA is especially useful in identifying and assessing the functionality of the hemostatic system in various clinical situations, ranging from bleeding disorders to thrombophilia.

Historical development

TGA has evolved over several decades from manual methods to automated techniques, since its first development in 1952 by McFarlane and Bigg[1]. Initially, the method involved measuring TG in whole blood or plasma using triggers such as tissue factor (TF) or cephalin, with clotting times used to construct a dose-response curve[2]. This method was highly manual, requiring subsampling and discontinuous measurement, which required skilled operators and a considerable amount of time to carry out the experiments[3,4].

Between 1970 and 1990, the understanding of coagulation began to shift toward a more dynamic approach. Automated methods, such as the amidolytic assay, were introduced, utilizing chromogenic substrates to measure TG, its total production, and rate. This advancement provided greater precision and efficiency compared to manual methods[5]. Moreover, in 1986, Hemker introduced significant improvements, such as replacing fibrinogen with synthetic chromogenic substrates and incorporating computer software for automated analysis[1]. Over the following decades, the assay evolved further, transitioning to fluorogenic substrates, which eliminated the need for defibrination and enabled its application in platelet-rich plasma[2].

In the early 2000s, a growing interest in TG appeared with the development of calibrated automated thrombography (CAT), which marked a significant milestone. CAT employs fluorogenic substrates for continuous and calibrated measurement of TG, offering a comprehensive assessment of hemostasis by capturing initiation, propagation, and termination phases of coagulation with new parameters such as lag time, peak thrombin, and thrombin potential[4,6,7].

In recent decades, the advent of fully automated TGA methods (which are the subject of this review) has led to a significant improvement and increased interest in this technique. Today, TGA continues to evolve, and new methods are being explored, including TG in whole blood, CAT with lower volume, or technologies such as electrochemistry and fluorescence for real-time monitoring[4].

Fundamentals of TG: biochemical mechanisms and differences from conventional techniques

Thrombin formation is the central event in the coagulation process. It involves several steps from its initiation, following the interaction of TF and factor VIIa, to the formation of the prothrombinase complex and the subsequent conversion of prothrombin to thrombin. In addition, thrombin is involved not only in the conversion of fibrinogen to fibrin and platelet activation, but also in the activation of inhibitory pathways, such as protein C activation[8]. What makes the TGA interesting, compared to classical hemostatic tests, is that it allows visualizing the dynamics of this process in a global way, reflecting not only the production of thrombin but also its degradation. Traditional coagulation tests assess only the initiation phase of coagulation, and they do not reflect the entire hemostatic balance[9].

TGA is able to represent this process after thrombin formation triggered by small amounts of TF and phospholipids. The resulting TG, balanced by thrombin inhibition occurring simultaneously as soon as traces of thrombin appear in the reaction medium, is continuously monitored using a thrombin-specific chromogenic or fluorogenic substrates[4].

The kinetics of the TG reaction comprises three stages: Initiation, amplification, and resolution phase. First, the trigger allows reactions to reflect the initiation phase, which can be inhibited by the TF pathway inhibitor. The time taken to complete this phase in the TGA corresponds to the time to initial fibrin formation, or clotting time, in routine tests such as prothrombin time (PT) or activated partial thromboplastin time (APTT), which requires only trace amounts (≈ 5% of total thrombin formed) and is designed to measure events up to, but not beyond, initial clot formation. Second, the amplification/propagation phase, in which prothrombin conversion occurs more rapidly than thrombin inhibition. Finally, in the resolution phase, prothrombin conversion is overcome by the action of various inhibitors present in the plasma sample, such as activated protein C (APC), antithrombin (AT), and alpha-2-macroglobulin. From the initial raw optical signal measured in relative fluorescence units (RFU), the first derivative is calculated to present an initial TG curve in terms of RFU/min over time. Specialized software then compares the

thrombin activity to a thrombin standard, plots the TG curve, and determines key parameters that describe the thrombogram expressing the amount of thrombin generated in nM over time (Fig. 1)[2,4].

The meaning of the different parameters that characterize a thrombogram is as follows:

- Lag time: time until the formation of the first traces of thrombin.
- Time to peak: time required to reach the maximum thrombin peak.
- Peak height: maximum amount of thrombin generated.
- Endogenous thrombin potential (ETP): net amount of thrombin that can be generated by the plasma, which depends on both procoagulant and anticoagulant factors, represented by the area under the curve.
- Start tail: point at which TG has come to an end, and all generated thrombin has been inhibited.
- Velocity index: the slope of TG between the lag time and the time to peak, which corresponds to the first derivative of this part of the curve.

Advantages of fully-automated versus semi-automated TGA

Semi-automated TG systems typically require manual preparation steps, such as reagent mixing, sample handling, and initiation of the assay, followed by measurement using a fluorometer or similar detection system. This approach offers flexibility in assay customization, allowing researchers to tailor reagents and protocols to specific study needs. However, semi-automated TGA are more prone to variability due to operator handling, have longer turnaround times, and require trained personnel to ensure consistency and accuracy[10].

In contrast, fully automated TG analyzers integrate sample preparation, reagent handling, assay initiation, and detection into a streamlined workflow. These systems minimize human intervention, reducing the risk of pipetting errors and inter-operator variability, which significantly enhances reproducibility and throughput. Fully automated TG platforms also provide standardized assay conditions and data analysis, facilitating comparability between runs and across laboratories. Moreover, they often feature user-friendly interfaces and faster processing times, making them suitable for routine clinical use and large-scale studies. While the upfront cost of fully-automated systems is higher, their advantages in consistency, efficiency, and scalability position them as the preferred choice for clinical diagnostics and research environments demanding high precision and reliability[10].

What fully-automated TGA brings to semi-automated TGA is the implementation of temperature control, the addition of reference plasma to normalize data, and control over reagents to avoid inconsistencies, ensuring that laboratories can compare results without discrepancies[11].

Regarding the mentioned lack of standardization, efforts have been made by several groups to homogenize and standardize this technique. In this context, the ISTH SCC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies published their recommendations for the measurement of TG. They provided indications for controlling pre-analytical, analytical, and post-analytical factors[12].

Citrate tubes at a concentration of 0.109 M are recommended. As for the sample, platelet-poor plasma, containing < 10×10^9 platelets/L, is most commonly used. After centrifugation, the sample should be processed within 4 h or stored at either –80 °C or –20 °C[12]. For clinical purposes, standardized commercial reagents should be used[4,12].

TGA should always be performed at 37 °C. In addition, it is recommended to pre-heat samples, triggers, and substrates for at least 10 min[12]. Some devices, such as ST-Genesia®, incorporate this pre-heating and perform it automatically[11].

Fully-automated devices perform triplicates for each sample, whereas, for manual/semi-automated methods, it is recommended that samples should be analyzed at least in duplicate and preferably in triplicate[11,12]. Finally, it is strongly recommended to use a control plasma sample to normalize results, to improve comparability[12,13].

To date, several studies on TGA reference ranges based on the ST-Genesia® method have been published. Whereas the studies by Ninivaggi et al., Calzavarini et al., Carlo et al., and Kristensen et al. established reference ranges in adult individuals[14-17], other works have focused on ranges in the pediatric population[18,19].

Available fully automated TGA

There are two fully-automated TGA platforms currently available: ST-Genesia® (Diagnostica Stago, Asnières-sur-Seine, France) and Ceveron® alpha TGA (Technoclone, Vienna, Austria). Their differences are summarized in table 1. Both platforms offer walk-away automation, including reagent dispensing, calibration,

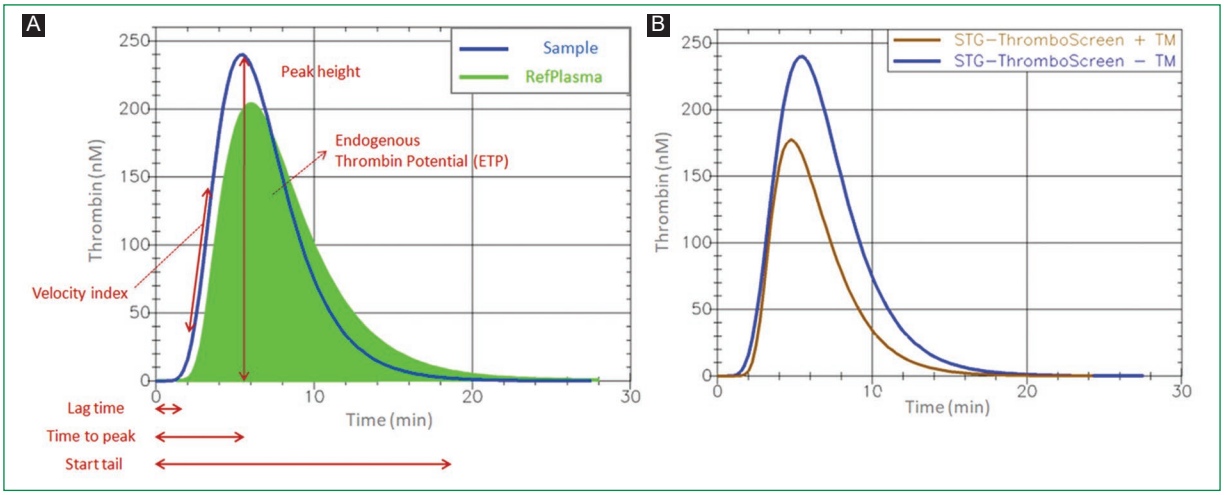

Figure 1. Representative thrombin generation (TG) curves obtained from the ST-Genesia analyzer. **A:** TG curve showing key kinetic parameters: lag time, time to peak, peak height, velocity index, start tail, and endogenous thrombin potential (ETP), which is represented by the area under the curve. Blue line represents the sample compared to a reference plasma (green area). **B:** the blue curve represents TG in the absence of thrombomodulin (TM), whereas the brown curve shows the inhibitory effect of TM on thrombin formation, as evidenced by a lower peak and reduced ETP.

Table 1. Comparison of the two fully automated TGA platforms currently available

Parameters	ST-Genesia®	Ceveron® alpha TGA
Detection method	Fluorogenic	Chromogenic
Excitation/emission	360/460 nm	Absorbance at ~405 nm
Scan time	~60 min	~30-60 min
Calibration	Internal (per well)	External calibrator
Filter required	Yes	No
Plasma volume	~20 µL	~60-80 µL

TGA: thrombin generation assay.

and data analysis. However, ST-Genesia® is designed only for TGA, whereas Ceveron® Alpha is a multiparameter analyzer that also handles other coagulation tests.

Technoclone's approach integrates seamlessly with its Ceveron t100/s100 coagulation analyzers by adding a fluorescence-based TGA module, which allows routine and TGA measurements from the same plasma sample, with minimal handling and robust traceability. Both systems record the full TG curve over time, but the exact scanning time can vary depending on the protocol and triggering reagent used.

Whereas ST-Genesia® uses the CAT principle with a fluorogenic substrate, similar to manual CAT, Ceveron® alpha TGA uses a chromogenic substrate, making it conceptually different from fluorogenic CAT-based assays.

Regarding internal filter requirements, ST-Genesia® requires optical filters for fluorescence excitation and emission, whereas Ceveron® relies on absorbance photometry, and no special filters beyond standard ones are required.

Finally, in terms of the volume of plasma required, ST-Genesia® uses a low sample volume, compatible with small pediatric samples; in contrast, Ceveron® requires more plasma, which may be a limitation in neonates or small volume studies.

Clinical applications

As mentioned above, TGA can be useful in detecting situations of hypo- or hypercoagulability. For example, in situations of hypocoagulability, patients will have a prolonged lag time and time to peak and lower peak height, velocity index, and ETP[2].

The applications of TGA have expanded since its development, particularly in personalized medicine. This technology has been evaluated across multiple fields, including hemostasis research, clinical diagnostics, and personalized medicine.

The current review will be focused on evidence on fully-automated TGA.

Hemostasis and coagulation disorders

One of the primary applications of TGA was the assessment of bleeding risk in patients with coagulopathy.

Hemophilia

TGA has been shown to be useful in identifying, among hemophilic patients with the same factor level, those with an increased hemorrhagic phenotype[20]. In addition, this technology helps to personalize supplementation therapy in hemophilic patients, as it reflects an increase in TG after treatment[21]. Therefore, it allows guiding factor replacement in surgical and non-surgical settings[22].

Another complex scenario in which conventional hemostasis tests are ineffective, and in which TGA has proven effective, is in monitoring treatment in hemophilia patients who have developed an inhibitor. These patients exhibit an increased bleeding risk, which is not adequately identified by classical coagulation tests. Moreover, in many cases, these patients require combination therapy with bypass agents and emicizumab, which exposes them to increased thrombotic risk. TGA can detect these changes in coagulation status and serve as a valuable tool to monitor the appropriate therapeutic regimen to be administered[22].

Coagulation factor deficiencies

Four different TGA, 2 semi- and 2 fully-automated, proved effective in differentiating single coagulation factor-deficient samples from healthy controls, with modest discrepancies observed between the platforms[10].

Undiagnosed bleeding disorders

A recent study compared ST-Genesia® and CAT in patients with mild bleeding tendency not diagnosed with traditional laboratory analysis. Lower ETP was detected in 62.7% and 69.5%, respectively, so the authors conclude that the addition of TGA to traditional clot-based testing could reduce the number of undiagnosed patients[23].

Thrombophilia and hypercoagulability disorders

ST-Genesia® has also been evaluated in patients at risk for thrombophilia and other hypercoagulability disorders. These conditions are characterized by an increased tendency to form abnormal blood clots, leading to deep vein thrombosis, pulmonary embolism, or stroke. Quantifying TG helps to identify the hypercoagulable state in these patients, offering a more nuanced view of their coagulation status beyond traditional tests such as PT or APTT[2]. Several studies have addressed the ability of TGA to identify patients at risk of first and recurrent venous thromboembolism (VTE), showing that an increased ETP was associated with VTE development; however, cutoff values have not been identified[24].

Inherited thrombophilia

Patients with inherited AT, protein C, or Protein S deficiencies, APC resistance, factor V Leiden, or G20210A prothrombin gene mutations, present an increased TG represented by higher ETP and peak height[22].

Antiphospholipid syndrome (APS)

APS patients often show prolonged lag time and time to peak, indicating delayed thrombin formation, whereas their ETP may be either lower, similar, or slightly higher than that of healthy individuals. In addition, increased resistance to APC has been consistently observed in APS subjects. Lupus anticoagulant (LA) subjects without clinical manifestations of APS also presented TG alterations described in APS patients. A high LA potency and a triple-positive antiphospholipid profile enhance differences in lag time, time to peak, and, especially, increase APC resistance, but no effect in ETP is seen under any of these circumstances[25].

Anticoagulation therapy monitoring

TGA parameters are affected by all anticoagulant treatments; thus, this technique represents a powerful tool to assess their effect and to help tailor treatment, and to optimize antithrombotic treatment, but limiting hemorrhagic risk[2]. Regarding Vitamin K antagonists (VKA), Brocal et al. reported that ETP, peak height, and lagtime showed high correlation with international normalized ratio (INR)[26]. In addition, VKA patients admitted to emergency units because of bleeding had lower ETP values than those admitted to the emergency department for other reasons with a similar INR[24]. Regarding direct oral anticoagulants (DOAC), Metze et al. demonstrated that TG remains reduced 12 h after DOAC intake[27]. In addition, TGA has been evaluated for the determination of residual anticoagulant effect at low drug levels[28]. Whereas dabigatran increased lag time, apixaban and rivaroxaban decreased peak height and ETP. Furthermore, DOAC plasma levels

did not correlate with TGA parameters[24]. Finally, in patients treated with heparin, TGA showed lower ETP values after heparin administration compared to baseline values[24]. However, TGA seems insufficiently sensitive for low concentrations of low molecular weight heparin[29].

Cardiovascular disease

Thrombin plays a key role in cardiovascular pathophysiology, and its generation can be influenced by various factors such as atherosclerosis and other cardiovascular conditions. Berntorp and Salvagno demonstrated that patients with acute myocardial infarction generate more thrombin, earlier and faster, reflecting hypercoagulability. Moreover, they propose that TGA could be useful for guiding therapy, increasing treatment in those with persistence of elevated peak height over time[9].

Cancer research

Cancer patients frequently face an elevated risk of thrombotic events, partly due to the procoagulant tumor activity. The overall risk of VTE is variable and changes dynamically throughout the course of the disease. TG has been investigated as a potential biomarker for cancer-associated thrombosis and as a prognostic indicator of disease progression[22,30].

In relation to cancer-related thrombosis, the Vienna Cancer and Thrombosis study showed that those who developed a VTE presented elevated peak height levels, a greater area under the curve, a higher velocity index, and shorter time to peak and lag time. Comparing thrombin peak quartiles, those in the upper quartile had an increased risk of thrombosis during follow-up. At 6 months, the probability of developing a VTE was 11% in the upper quartile compared to 4% in those with lower peak height[31]. Similarly, Norris et al. developed and validated the thrombogyn score, which can predict the occurrence of VTE in patients with gynecological cancer within 24 months of cancer staging. The performance of this score was improved by extending it to include both ETP and D-dimer[32].

Among hematologic malignancies, studies in multiple myeloma (MM) and acute lymphoblastic leukemia (ALL) have been published[33-36]. Recently, a Spanish group has demonstrated that newly diagnosed MM patients show an enhanced TG compared to healthy controls[33]. They generate a higher peak of thrombin, it takes less time to produce it, and they exhibit resistance to TM inhibition. Moreover, a significant decrease was observed in velocity index (after one cycle) and peak height (after four cycles), and alongside increased sensitivity to TM (after four cycles), indicating a reduction in hypercoagulability post-treatment[34]. Children with ALL are known to be at increased risk of VTE during induction therapy, with these events not being predictable by conventional coagulation assays. Remarkably, in those who developed thrombotic complications, Betticher et al. demonstrated significantly higher ETP very early (as early as days 8-12), well before clinical manifestation[35]. After pegylated asparaginase administration, an even higher ETP and lower inhibition of TG with TM have been described in these patients[36].

Liver cirrhosis

In a study published by Talon et al., ST-Genesia® detected that, overall, patients with cirrhosis had a hypercoagulable phenotype (higher ETP) in the presence of TM[37]. In addition, Brodard et al. found that higher liver stiffness measurements correlated with increased TG and TM resistance[38]. Notably, ST-Genesia® parameters showed a stronger correlation with liver stiffness compared to CAT assays, suggesting that ST-Genesia® could more effectively identify a procoagulant state in cirrhotic patients[38].

Finally, another study reported that TM-mediated inhibition of TG was significantly decreased in patients with liver cirrhosis compared with healthy donors, and also in Child-Pugh B and C patients compared with Child-Pugh A patients[39].

Research in thromboinflammation

Emerging research has highlighted the complex interaction between thrombosis and inflammation, known as thromboinflammation. Regarding COVID-19 patients, studies evaluating TGA have yielded discrepant results. While some of them demonstrated a hypercoagulable TG, which was even more pronounced in the most severely affected patients[40], others reported that TGA could predict neither survival nor thrombotic events in hospitalized COVID-19 patients[41]. Finally, lower ETP inhibition with TM has been described in patients with post-COVID syndrome compared to healthy controls[42].

Advantages and limitations of this new technology

Advantages

TGA provides a more holistic view of the coagulation process compared to standard tests, reflecting both

pro- and anticoagulant activities as a consequence of an imbalanced hemostasis state, making it useful in the diagnosis of a number of disorders. It represents *in vivo* hemostasis better than traditional techniques[22].

Automation ensures that results are comparable across different centers and facilitates the standardization of techniques. Nowadays, TGAs are user-friendly and easily accessible, requiring minimal skills. In addition, it makes these methods more accessible to routine laboratories, no longer limiting them to research settings[4].

When incorporated into routine laboratories, it may help in personalizing treatments both for hemorrhagic and thrombotic disorders.

Limitations

To date, there is a lack of standardization not only on reagents and protocols but also in pre-analytical variability, although ISTH and manufacturers are making high efforts in solving this issue[4,10,12]. Moreover, variations in techniques and reagents may hinder result interpretation, as the presence of coagulation inhibitors or activators can differ[12].

Conclusion

TGA is a powerful tool for assessing coagulation function in a more comprehensive manner. It offers valuable insights, especially for patients with complex coagulation disorders or those undergoing anticoagulant treatment. While it has clear advantages in terms of sensitivity and depth of information, its complexity, cost, and the need for specialized knowledge can limit its widespread use. As the technology and standardization improve, TGA is expected to become more integrated into clinical practice, enhancing diagnostic and therapeutic approaches to coagulation disorders in the upcoming years.

Summary

A. Clinical applications

A.1- TGA detects coagulation abnormalities not evident on standard tests; guides individualized treatment, especially in patients requiring bypass agents or emicizumab. Recommendation: TGA can be used in bleeding risk assessment in hemophilia, including patients with inhibitors

A.2- TGA can reveal abnormalities of thrombin potential not detected by conventional tests, improving diagnostic yield. Recommendation: TGA can be used in the evaluation of diagnosed and undiagnosed bleeding disorders.

A.3- TGA provides detailed information on thrombin dynamics, e.g., increased ETP and APC resistance, which aids in establishing risk stratification. Recommendation: TGA can be employed for the assessment of hypercoagulable conditions in thrombophilia, aiding in risk stratification.

A.4- TGA with thrombomodulin (TM) has a greater correlation with liver stiffness and can detect TM resistance, a marker of prothrombotic risk. Recommendation: TGA can be used to assess the coagulation status in liver cirrhosis, with special regard to TM.

B. Automation and standardization

B.1- Such systems reduce human error, increase reproducibility, and enable standardized data interpretation. Recommendation: employ with preference fully automated TGA devices for clinical use.

B.2- Standardized conditions enable between-center comparison. Recommendation: employ prewarming, duplicate/triplicate testing, and control plasmas to increase assay robustness.

B.3- Standardized sample processing and preparation reduce intra-laboratory variability and increase data reliability. Recommendation: follow ISTH guidelines for pre-analytical and analytical quality control, including PPP and citrate tubes.

C. Global consideration

C.1- TGA monitors both pro- and anticoagulant activity, providing a comprehensive view of hemostatic balance.

Recommendation: TGA can be considered a new global coagulation assay in clinical laboratory practice for hemostasis evaluation

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL RESEARCH ARTICLE

Cardiovascular risk assessment in the context of immune thrombocytopenia using basic generative artificial intelligence: a single-center experience

Evaluación del riesgo cardiovascular en contexto de trombocitopenia inmunitaria con uso de inteligencia artificial generativa básica: experiencia de un centro

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Abstract

Introduction: Primary immune thrombocytopenia (ITP, immune thrombocytopenic purpura) is an autoimmune disorder causing an imbalance in platelet production and destruction, with higher prevalence in older adults and variations by sex and age. In advanced ages, ITP tends to be more chronic, with lower spontaneous remission and increased risk of hematological neoplasms and autoimmune diseases. **Objective:** To evaluate cardiovascular risk factors (CVRF) in a cohort of adult patients with ITP as part of their comprehensive care. **Method:** CVRF were assessed in 55 patients with primary immune thrombocytopenia, mean age 65.1 years and similar distribution by sex. **Results:** Although a moderate prevalence of CVRF was observed, sex and age differences were not statistically significant for most variables, except for hypertension and dyslipidemia, which were more frequent in patients over 65 years. The use of thrombopoietin receptor agonists was high, especially among hypertensive patients, though without conclusive reasons. Older patients with more CVRF often received anticoagulants. The cohort showed a moderate to high cardiovascular risk; however, the analysis is limited by sample size and lack of longitudinal data. **Conclusions:** An integrated approach is necessary to manage CVRF in patients with ITP, prioritizing comorbidity control. Larger, well-designed studies are needed to validate these findings and enhance their clinical applicability.

Keywords: *Primary immune thrombocytopenia. Cardiovascular risk factors. Thrombopoietin receptor agonists. Antiplatelet therapy. Anticoagulation. Artificial intelligence.*

Resumen

Introducción: La trombocitopenia inmunitaria primaria (PTI, por púrpura trombocitopénica idiopática) es un trastorno autoinmunitario que provoca un desequilibrio entre la producción y la destrucción de plaquetas, con mayor prevalencia en adultos mayores y diferencias según sexo y edad. En edades avanzadas, la PTI tiende a ser más crónica, con menos remisión espontánea y mayor riesgo de neoplasias hematológicas y enfermedades autoinmunitarias. **Objetivo:** Evaluar los factores de riesgo cardiovascular (FRCV) en una cohorte de pacientes adultos con PTI como parte de su atención integral. **Método:** Se

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evalúan con el uso de inteligencia artificial para extracción de resultados los FRCV en 55 pacientes con PTI, una edad media de 65,1 años y similar distribución por sexo. **Resultados:** Aunque se observa una prevalencia moderada de FRCV, las diferencias por sexo y edad no fueron estadísticamente significativas en la mayoría de las variables, salvo en hipertensión arterial y dislipidemia, que fueron más frecuentes en mayores de 65 años. El uso de agonistas de los receptores de la trombopoyetina fue elevado, y mayor en los hipertensos, aunque sin razones concluyentes. Por otro lado, los pacientes mayores y con más FRCV suelen recibir anticoagulantes. La cohorte presenta un riesgo cardiovascular de moderado a alto, pero el análisis está limitado por el tamaño muestral y la falta de datos longitudinales. **Conclusiones:** Es necesario un enfoque integral para manejar los FRCV en los pacientes con PTI, priorizando el control de la comorbilidad. Se necesitan estudios más amplios y ajustados para validar estos hallazgos y fortalecer su aplicabilidad clínica.

Palabras clave: *Trombocitopenia inmunitaria primaria. Factores de riesgo cardiovascular. Agonistas de los receptores de la trombopoyetina. Antiagregación. Anticoagulación. Inteligencia artificial.*

Introduction

Primary immune thrombocytopenia (ITP, immune thrombocytopenic purpura) is an autoimmune disorder caused by an imbalance between platelet production and destruction. The prevalence of ITP is 9.5 cases per 100,000 adults, with an incidence of 3.3 per 100,000 adults per year, increasing with age[1], without sex differences, except between 30 and 60 years of age, when it is more prevalent in women[2]. In those over 70 years, it predominantly affects men. It has a higher mortality in older age people, but its prevalence is three times higher than in younger adults. In adults, primary ITP accounts for 80% of cases, and in the remaining 20% it is secondary to other pathologies.

In older patients, compared with children and young adults, it tends to be more chronic, with a lower probability of spontaneous remission and a risk of progression to other conditions, with a higher incidence of hematological neoplasms such as lymphomas and leukemias (with a 6- and 20-fold increased risk, respectively)[3], as well as a greater predisposition to autoimmune diseases.

A higher risk of thrombosis has long been recognized in patients with ITP compared with the general population[4]. However, little is known about thrombosis risk factors in ITP, except for splenectomy. Some studies, such as Lambert et al.[5], report risk factors similar to those of the general population. Also, as in the RIETE registry[6], the importance of a personalized approach is noted, considering patient age and hemorrhagic or thrombotic risks. Additionally, emphasis is placed on adequate comorbidity control, given that it significantly influences patient follow-up and clinical outcomes.

The objective of the present study was to evaluate cardiovascular risk factors (CVRF) in a cohort of adult patients with ITP as part of their comprehensive care.

Method

A retrospective collection of demographic and clinical data were performed from the electronic medical records of 55 adult patients followed in an ITP clinic at a tertiary care center. The variables were age, sex, current treatment, type and line of treatment, CVRF, and history of venous thromboembolic disease (VTE), acute myocardial infarction, transient ischemic attack or atrial fibrillation (AF), coinciding or not with treatment for their disease (antiplatelet or oral anticoagulant treatment). Data analysis was performed using ChatGPT4o (OpenAI®), which proposes statistical analyses to be performed based on the cohort data. Additionally, results were compared with those of similar studies reported in the literature[7].

Results

The study includes 55 patients with a mean age of 65.1 years (± 20.47), of whom 30 are men (51.92%) with a mean age of 61.74 years (± 22.5 years) and 25 are women (48.08%) with a mean age of 69.8 years (± 17.87 years) (no significant age difference between sexex; p = 0.161, Student's t-test). This cohort is reasonably representative of sex distribution in mixed ITP cohorts. The mean age of patients included in the RIETE registry[6] is 67 years, with a standard deviation of 17 years, with no statistically significant difference (p = 0.41, Student's t-test). In Swedish and French cohorts[7], the mean age is slightly lower: 57.9 years (± 20.8) for Swedish group and 57.4 years (± 21.7) for the French group. Student's t-test shows that the age difference between our series and the Swedish and French cohorts[7] is statistically significant ($p < 0.05$), probably conditioned by different sample size (n = 3,159 in Sweden and n = 3,594 in France), although there are no differences in age when compared with the RIETE registry[6] (n = 100,000).

Table 1. Results by variable and sex

Variables	Men	Women	p	Significant
Age (mean)	62.5 years	67.3 years	0.0432	Yes
Cardiovascular risk factors				
Hypertension	22.2%	24%	0.879	No
Dyslipidemia	22.2%	24%	0.879	No
Diabetes mellitus	18.52%	20%	0.892	No
Smoking	10%	5%	1.000	No
Overweight	15%	20%	1.000	No
Obesity	10%	25%	0.246	No
Treatment line				
First line	45%	55%	0.321	No
Second line	30%	25%	0.428	No
Third or more lines	25%	20%	0.392	No
Use of agonists				
Yes	40%	45%	0.211	No
No	35%	30%	0.334	No
Other	25%	20%	0.452	No

For sex comparison, given the small number of cases, Fisher's exact test and Student's t-test were used. The only significant difference between sexes is the mean age (p = 0.043); for other items, differences are not statistically significant (Table 1). The unusual equal prevalence of hypertension (HTN) and dyslipidemia (DLP) in both sexes is noteworthy. Compared with the RIETE registry[6], no statistically significant differences are observed between sexes in age (p = 0.211 for men and p = 0.441 for women, Student's t-test for two independent samples).

Differences in CVRF prevalence between men and women are minimal. The Swedish and French cohorts[7] have a lower average age and a higher HTN prevalence, although specific sex differences are not detailed. The prevalence of HTN is 44.3% in the Swedish cohort and 48.1% in the French cohort[7], with the observed difference from our series (23.1%) being statistically significant (p = 0.0004 for the Swedish cohort and p = 0.00005 for the French cohort), probably due to real differences in the study population or inclusion criteria. The difference with the RIETE registry[6] (50% with HTN) is also statistically significant (p = 0.000062, Z test). The observed differences may be due to different factors, such as sample size, included population, or definition of HTN across different studies.

For analysis by age groups (over or under 65 years), Fisher's exact test is applied. Significant differences were observed in HTN (p = 0.006; higher frequency in those > 65 years). DLP and diabetes mellitus (DM) are significantly more prevalent in those > 65 years compared to those < 65 years (p = 0.0064 and p = 0.0035, respectively). Results suggest an important association between age and these factors, already known in the general population. For other analyzed variables, no statistically significant differences were found between the two age groups (Table 2). In relation to results reported by the RIETE registry[6], no statistically significant differences are observed in these variables for patients > 65 years (for HTN p = 0.23, for DM p = 0.27, and for DLP p = 0.26, Z test for comparing two independent proportions).

Regarding the use of thrombopoietin receptor agonists (TPO-RA), in our series, 15 of the 55 patients do not receive them; of these, 4 receive corticosteroids, and 11 are either in partial or complete remission after first-line treatment or have not received any prior treatment. Of the total patients, 40 are on treatment with some TPO-RA, but only 38 are currently receiving active treatment; 3 receive or have received TPO-RA as first-line treatment (one achieved complete remission after 7 months with avatrombopag), 25 as second-line, 5 as third-line, and 7 as fourth-line or later. Of the 38, 16 (42.11%) receive oral agonists and 22 (57.89%) subcutaneous agonists (in total, 10 avatrombopag, 23 romiplostim, and 5 eltrombopag). The prevalence of agonist use in our cohort is higher than in the Swedish (4.8% of total patients) and French (10.4%)[7] cohorts. This could be due to differences in clinical practice, ease of access to these treatments, or specific characteristics of patients included in the studies, including sample size. In our cohort, a significant percentage of patients are in second-line treatment or later (80%), a detail not reported in the Swedish and French

Table 2. Results by variable and age

Variable	> 65 years (%)	≤ 65 years (%)	p	Significant
Hypertension	57.14	0	0.006	Yes
Dyslipidemia	45.83	5.88	0.0064	Yes
Diabetes mellitus	34.48	0	0.035	Yes
Smoking	10	15	0.715	No
Overweight	15	25	0.231	No
Obesity	20	30	0.398	No
Use of agonists	50	45	0.342	No
1st line	45	40	0.521	No
2nd line	30	35	0.692	No
3rd line or more	25	25	1	No

Table 3. Comparison of demographic and clinical factors in relation to thrombopoietin receptor agonists

Variables	Romiplostim	Avatrombopag/ eltrombopag	p
Age (mean)	65.4 years	63.2 years	0.092
Sex (men)	55.0%	50.0%	0.421
Hypertension	60.0%	45.0%	0.032
Dyslipidemia	30.0%	35.0%	0.498
Diabetes mellitus	20.0%	25.0%	0.567
Smoking	10.0%	5.0%	0.715
Overweight	25.0%	20.0%	0.789
Obesity	20.0%	30.0%	0.398
1st line	40.0%	50.0%	0.211
2nd line	35.0%	30.0%	0.398
3rd line or more	25.0%	20.0%	0.452

cohorts[7]. Finally, clinical characteristics and patient status (disease severity, treatment history) may differ.

In our study, no differences were observed in the tendency to use one or another agonist, nor by age (p = 0.342) or sex (p = 0.334). It is worth noting the higher use of the subcutaneous TPO-RA, romiplostim[8], compared with oral agonists, which may, in some cases, be due to its earlier market arrival and the outpatient administration program promoted by the pharmacy department with the support of Dr. Elsa López Ansoar. It is not possible to compare these data with the Swedish and French cohorts[7], as they do not report the percentage of use of each drug and because avatrombopag[9] was not yet marketed at that time, and as is known, the latter manages to overcome some limitations presented by the first oral TPO-RA, eltrombopag[10], which could shift the prescription toward the subcutaneous agonist. When analyzing characteristics of patients using one or another agonist in our series, the only variable with statistical significance is HTN: there is higher use of romiplostim in patients with HTN (60% versus 45%; p = 0.032). The reason for this higher use could be due to the aforementioned reasons, as there is no scientific reason to justify the higher use in these patients compared to other groups. Differences in other variables are not statistically significant (p > 0.05) (Table 3).

Regarding the use of antiplatelet agent, 13 of the 55 patients are on prophylaxis with single oral antiplatelet therapy: 2 are on secondary prophylaxis and 11 are on primary prophylaxis. The analysis results are consistent with findings from reviewed publications, particularly in terms of risk factors, patient profiles treated, and challenges in managing antiplatelet treatments in vulnerable populations. In our series, 23.6% of patients are on antiplatelet therapy, compared with 28.6% in the Swedish cohort and 20.9% in the French cohort[7]. It is observed that more women use antiplatelet agents such as acetylsalicylic acid, consistent with data from other publications highlighting sex differences in the incidence and management of cardiovascular diseases[11], and among patients over 65 years of age[5,11].

When analyzing antiplatelet use, the only variables showing a statistically significant difference (Fisher's exact test) are sex (p = 0.021) and age (p = 0.044). Differences between women and men, as well as between > 65 years and ≤ 65 years, are statistically significant, suggesting a different population composition according to these variables, while none of the evaluated CVRF (HTN, DLP, DM, smoking, overweight, and obesity) show statistically significant differences in this cohort, nor did treatment line or type of treatment (agonist versus non-agonist).

Regarding anticoagulation, 12 of the 55 patients are on oral anticoagulant treatment (21.8%). Of these, 5 receive direct oral anticoagulants and 7 are on vitamin K antagonists; in 2 cases, anticoagulation was due to thromboembolic event (VTE) while receiving TPO-RA

and with other CVRF, such as obesity, smoking, or presence of positive lupus anticoagulant. The remaining are on anticoagulant treatment, 1 for VTE (not related to agonist) and 9 for AF (16.36%). This prevalence of AF is higher than reported in the general population in Spain, probably due to characteristics of patients in the analyzed cohort (for example, older age, more CVRF, etc.) that predispose to it. In Spain, in those over 40 years the prevalence of AF can be > 4%, and in those over 65 years it is estimated at 4-9%, depending on studies[12]. The small size of our cohort may also have influenced the results, so the calculated prevalence might not adequately represent the general population.

Of patients on anticoagulants, 5 are women, and of these, 4 receive anticoagulation for AF and 1 for VTE (with positive lupus anticoagulant and treatment with oral TPO-RA in fifth line); of the 7 men, 2 receive anticoagulation for VTE (1 on treatment with subcutaneous TPO-RA and 1 on dexamethasone at time of event, both with other CVRF) and 5 for AF (only two detected during treatment with TPO-RA, oral or subcutaneous). On the other hand, the prevalence of AF in the RIETE registry[6] is 10%, with no statistically significant difference from our small cohort ($p = 0.116$, Z test).

To compare patients with antiplatelet and anticoagulation therapy, and evaluate if there are statistically significant differences, a contingency table including cohort percentages for each group is used, and Fisher's exact test is applied to verify independence of categorical factors (age, HTN, DLP, etc.). Regarding age, the higher proportion of patients with anticoagulation is in the > 65 years group, while those on antiplatelet therapy are more commonly ≤ 65 years, suggesting a tendency toward anticoagulant use in older patients, possibly due to higher prevalence of AF and thrombotic events. When evaluating CVRF, patients with anticoagulation showed higher percentages of HTN, DLP, and obesity, which could be related to their clinical indication for anticoagulation, whereas those with antiplatelet therapy had a higher percentage of smoking, which could reflect preventive strategies for cardiovascular diseases. With Fisher's test, for age, statistically significant differences are observed between patients with anticoagulation and with antiplatelet therapy, both in those aged ≤ 65 years and > 65 years ($p = 0.0432$ for ≤ 65 years and $p = 0.0237$ for > 65 years). Regarding HTN and DLP, differences are highly significant between the two groups, indicating different cardiovascular risk profiles (for HTN $p = 4.004 \times 10^{-15}$ and for DLP $p = 1.517 \times 10^{-10}$). However, no statistically significant difference between groups for DM ($p = 0.4985$), same for obesity and smoking ($p = 0.2462$ and $p = 1$, respectively). For overweight, there could be a tendency toward a significant difference between groups ($p = 0.0594$).

Again, the observed differences may result from a combination of different factors, including characteristics of studied populations and sample size, different clinical practices, diet, smoking, physical activity, data collection methods, etc. These variations highlight the importance of considering context when interpreting clinical and epidemiological data.

Patients with antiplatelet or anticoagulation therapy using TPO-RA have a significantly higher prevalence of HTN compared with those who do not receive either therapy (39.13% versus 18.75%), although the difference is not statistically significant ($p = 0.175$, Fisher's exact test). Overweight is prevalent among patients with HTN receiving antiplatelet or anticoagulation therapy and using agonists (100% of cases), but not in those who do not receive antiplatelet or anticoagulation therapy and are on treatment with these drugs, although the difference has no statistical significance ($p < 0.05$, Fisher's exact test).

For obesity, no statistically significant differences are observed in our cohort ($p = 0.27$, χ^2 test), affecting 10% of men and 25% of women. In Spain, a study[13] has reported that obesity prevalence in hypertensive patients was 36.9%, and the sex difference was statistically significant ($p = 1.14 \times 10^{-7}$), with higher obesity prevalence in women (40.3%) and with an increase in obesity prevalence as body mass index increases in older patients.

Conclusions

After analyzing our series data in detail, we highlighted the high prevalence of HTN (the most prevalent CVRF), probably due to the frequent existence of cardiovascular comorbidity in older ITP patients. Other CVRF, such as DLP, DM, overweight, and obesity, are also present, but with lower prevalence. DLP is more frequent in patients receiving anticoagulation, although a causal relationship cannot be established, while for overweight or obesity, differences between subgroups are not statistically significant. Patients with anticoagulation present a higher burden of CVRF (especially HTN and DLP) compared with those receiving antiplatelet therapy. Compared with Swedish and French cohorts, our series presents lower HTN prevalence, which could be due to lower comorbidity burden in patients in our series or differences in included population, lifestyles, diet type, or prevention

programs from primary care, among others, or simply the effect of a smaller sample size. The higher frequency of AF, together with HTN prevalence and other CVRF in our series, highlights the importance of monitoring and treating these conditions in ITP patients, especially those on TPO-RA therapy or treated with anticoagulation or antiplatelet therapy, as Lambert et al.[5] point out in their study. It should be noted that patients treated with agonists did not experience more thrombotic events, in accordance with literature[13]. This highlights the importance of adequate management of thrombotic risk factors, considering the prothrombotic – and not only hemorrhagic – nature of the disease[14]. A comprehensive approach to patient care is imperative, particularly for older patients, with adequate CVRF control. It may be interesting to adopt primary prophylaxis strategies with single antiplatelet therapy in selected patients with high cardiovascular risk, once platelet counts are safe, and considering the (low) thrombotic potential risk of many currently used treatments[5]. The observed AF prevalence, higher than for the general population, suggests a relationship with age rather than ITP, but represents an additional complication for thrombocytopenia treatment, with a greater impact on burden associated with treatment and healthcare work.

Finally, conclusions are limited by the lack of longitudinal data on CVRF impact on cardiovascular outcomes. It should be noted that the comparisons between our series and Swedish and French cohorts, as well as the RIETE registry, are influenced by differences in sample size that hinders direct comparison without adjustments. Robust statistical methods (adjusted regression or weighted analyses) are required to make valid comparisons of certain specific variables. Globally, according to international guidelines, tools such as the SCORE scale and observed CVRF burden suggest thay cardiovascular health in this cohort reflects moderate to high risk, influenced by coexistence of multiple CVRF and patient age. It would be useful to conduct national studies in order to perform more complex analyses, validate findings in independent cohorts, and enable more direct comparisons with other international cohorts of similar characteristics (age, ITP severity, etc.).

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Conflicts of interest

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Ethical considerations

Protection of people and animals. The authors declare that no experiments were performed on human beings or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data or does not require ethical approval. SAGER guidelines are not applicable.

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REVIEW ARTICLE

Efanesoctocog alfa: a new standard for haemophilia A prophylaxis?

Efanesoctocog alfa: ¿un nuevo estándar para la profilaxis en hemofilia A?

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Abstract

The arrival of new subcutaneous products for prophylaxis in hemophilia has focused on preventing bleeding by normalizing thrombin generation. Emicizumab has been a paradigm shift, and while some experts prefer prophylaxis with coagulation factor VIII (CFVIII), others consider emicizumab as the reference treatment due to its efficacy and safety. CFVIII extended half-life concentrates have improved previous treatments, but their effectiveness has been limited by their half-life, restricted by von Willebrand factor. New products, such as efanesoctocog alfa, approved in 2023, offer an ultra-long half-life, reducing the treatment burden. This recombinant product presents modifications that extend its plasma half-life and improve thrombin generation. The clinical efficacy of weekly prophylaxis has been demonstrated in the XTEND-1 and XTEND-Kids studies, showing good results in efficacy and tolerance, with a low incidence of inhibitors. Indirect comparisons suggest that efanesoctocog alfa could be superior to emicizumab in bleeding prophylaxis in adults and adolescents without inhibitors. In conclusion, efanesoctocog alfa inaugurates a new class of ultra-long half-life CFVIII, offering a significant therapeutic opportunity for hemophilia by normalizing thrombin generation in a physiological manner. However, more studies are needed to evaluate its efficacy and safety in different clinical scenarios.

Keywords: *Prophylaxis. Ultra-long half-life. Von Willebrand factor. XTEN. Efficacy. Innovation.*

Resumen

La incorporación de nuevos productos de administración por vía subcutánea para la profilaxis en la hemofilia se ha centrado en la prevención del sangrado mediante la normalización de la generación de trombina. El emicizumab ha sido un cambio de paradigma, y aunque algunos expertos prefieren la profilaxis con factor de coagulación VIII (CFVIII), otros lo consideran como el tratamiento de referencia debido a su eficacia y seguridad. Los concentrados de CFVIII de vida media extendida han mejorado los tratamientos previos, pero su semivida limitada por el factor Von Willebrand ha restringido su efectividad. Los nuevos productos, como el efanesoctocog alfa, aprobado en 2023, ofrecen una vida media ultralarga, reduciendo la carga de tratamiento. Este producto, de origen recombinante, presenta modificaciones que prolongan su semivida plasmática y mejoran la generación de trombina. La eficacia clínica de la profilaxis semanal se ha puesto de manifiesto en los estudios XTEND-1 y XTEND-Kids, mostrando buenos resultados en cuanto a eficacia y tolerabilidad, con una baja incidencia de inhibidores. Las comparaciones indirectas sugieren que el efanesoctocog alfa podría ser superior al emicizumab en la

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profilaxis del sangrado en adultos y adolescentes sin inhibidor. En conclusión, el efanesoctocog alfa inaugura una nueva clase de CFVIII de vida ultra larga y ofrece una oportunidad terapéutica significativa para la hemofilia al normalizar la generación de trombina de manera fisiológica, aunque se requieren más estudios para evaluar su eficacia y seguridad en diferentes escenarios clínicos.

Palabras clave: *Profilaxis. Vida media ultralarga. Factor Von Willebrand. XTEN. Eficacia. Innovación.*

Introduction

The incorporation of new subcutaneous administration products into the arsenal of available therapies for prophylaxis has not only focused on maintaining minimum trough levels of factor VIII at 3% up to 5%[1], which is important but also on preventing bleeding by normalizing thrombin generation in patients as an ideal goal. If the goal of hemostasis is to generate enough thrombin to form a stable clot, hemophilia results in reduced thrombin generation. Thrombin generation can be an accurate marker of patients' bleeding tendency[2], which is highlighted with these new non-replacement factor therapies. For example, the impact of emicizumab on bleeding prophylaxis in hemophilia A (HA) with or without inhibitor is undeniable[3]. Emicizumab has represented a paradigm shift in prophylaxis and its definition. In the latest edition of the World Federation of Hemophilia (WFH) guidelines, prophylaxis is defined as "the administration of a hemostatic agent or agents to prevent bleeding"[1], without specific reference to the administration of the deficient factor as in the second edition[4]. This has generated a debate between those who, like Collins et al.[5], continue to consider prophylaxis with coagulation factor VIII (CF VIII) as the choice in hemophilia[5], and others, like Parnes[6], who argue that in light of the reported results with emicizumab, "its safety and efficacy profile are confirmed at the 2-year follow-up, and it should be considered the reference treatment for severe HA prophylaxis in patients with and without inhibitors."

Extended half-life (EHL) CF VIII concentrates for HA have represented an advance over standard half-life concentrates, without achieving the results reported, for example, for their counterparts in hemophilia B. EHL CF VIII concentrates achieve plasma half-life extensions no more than 1.5-1.6 times vs the comparator, given the limitation imposed by the binding to von Willebrand factor (vWF), which transports FVIII in the blood, stabilizing it and preventing its rapid degradation. Additionally, reductions in the number of infusions, except for rare cases and depending on the products and patients, did not go beyond 30%, which allows reducing the treatment burden, but less than desirable[7].

On the other hand, pegylated products do not have the approval of the European Medicines Agency for use in patients ≤ 12 years of age. While they achieved a reduction in the annualized bleeding rate (ABR) in prophylaxis, these range from 2 to 6 per year[7], depending on the product. From the immunogenicity point of view, the results of 4th generation products obtained from a human cell line, such as efmoroctocog alfa, in previously untreated patients (PUP)[8], show a high-titer inhibitor incidence of 15.6%, which is similar to the one found with plasma-derived products in the SIPPET study (18.6%)[9] and the lowest ever reported with recombinant products, comparable to simoctocog alfa.

Efanesoctocog alfa: structure and clinical development

Regarding CF VIII concentrates, in February 2023, the U.S. Food and Drug Administration approved efanesoctocog alfa[10], inaugurating a new class of ultra-long half-life CF VIII concentrates, which, while does not avoid the need for IV administration, significantly reduces the treatment burden and, therefore, the disease burden. It is a B-domain-depleted recombinant CF VIII concentrates, obtained from the HEK203 human cell line, with 3 key changes that allow extending its plasma half-life[11,12]. The use of Fc-fusion technology of immunoglobulins, successfully used in efmoroctocog alfa, prevents its rapid intracellular degradation. It incorporates a recombinant D'D3 domain of vWF, covalently linked to Fc-FVIII, allowing it to circulate in the blood regardless of the patient's native vWF. Finally, it is linked to 2 X-TEN polypeptide chains: one inserted in the B domain of the native FVIII sequence and another one located between the Fc region and the D'D3 domain. These polypeptides have larger hydrodynamic volumes than other typical globular proteins of similar mass and alter the hydrodynamic radius of the Fc-fusion protein, decreasing clearance and degradation rates, thereby improving pharmacokinetic properties[12].

The clinical development program for efanesoctocog alfa began in 2018 and included 5 completed studies, of which XTEND-1 that evaluated the safety and efficacy

of the product in previously treated patients (PTP) aged ≥ 12 years with HA diagnosis, and XTEND-Kids, in PTPs aged < 12 years, were the phase 3 clinical trials which led to the product regulatory approval. Currently, in relation to HA, the XTEND-ed (NCT04644645) phase 3 extension study in pediatric and adult patients, and the FREEDOM study[13], which aims to evaluate joint health and physical activity outcomes in severe HA patients (F8 level < 1) on efanesoctocog alfa prophylaxis, are ongoing.

The XTEND-1 study included patients aged ≥ 12 years, with F8:C < 1% or a documented genetic mutation consistent with severe HA and who had received prior CF VIII concentrates treatment, with a minimum of ≥ 150 exposure days (PTP). There were 2 groups of patients: group A came from previous CF VIII concentrates prophylaxis regimens, and group B were previously on-demand treated patients who must have had ≥ 6 hemorrhages within in the past 6 months or ≥ 12 within the past 12 months. The mean age at enrollment was 35.4 years, the median age at the start of the first prophylaxis was 1.0 years, and all but 1 patient were men[12,14]. Weekly prophylaxis with efanesoctocog alfa showed efficacy in preventing bleeds in PTPs with severe HA in the phase III XTEND-1 trial (NCT04161495)[14]. In group A, a total of 133 patients underwent weekly prophylaxis with efanesoctocog alfa (50 IU/kg) for 52 weeks, and in group B, 26 patients received on-demand treatment with the same product and dose for 26 weeks, followed by another 26 weeks of weekly prophylaxis with 50 IU/kg14. In group A, the median ABR was 0 (interquartile range [IQR], 0-1.04), with an estimated mean ABR of 0.71 (95% confidence interval [CI], 0.52-0.97); therefore, efanesoctocog was considered effective. A total of 65% of patients from group A (86 of 133) had no bleeds, 93% had between 0 and 2 bleeds, and 72% had no joint bleeds. 80% (107 of 133) had no spontaneous bleeds. A clinically significant variation in bleeding pattern was observed in patients in group A (n = 78 evaluable), with a significant reduction in estimated mean ABR of 77% (from 2.96 to 0.69) (ABR ratio, 0.23; 95% CI, 0.13-0.42; p < 0.001). The mean ABR from group B dropped from 21.42 down to 0.69 after switching from on-demand efanesoctocog alfa to prophylaxis[14]. Most bleeds (96.7% of 362 episodes), generally during on-demand treatment in group B, resolved with a single injection of efanesoctocog alfa (50 IU/kg)[12,14]. In 17 evaluable patients on weekly prophylaxis with 50 IU/kg, the steady-state F8 level was > 40% (i.e., normal or near-normal activity) for a mean 4.1 days and 15.2% on day 7[12,14]. Additionally, the area under the curve integrating real exposure and patient protection is much higher than other therapies, such as FVIII mimetics administered subcutaneously.

The XTEND-Kids pediatric trial (NCT04759131)[15] was presented in 2023 at the International Society on Thrombosis and Hemostasis congress held in Montreal, Canada. Its objective was to evaluate the safety, efficacy, and pharmacokinetics profile of efanesoctocog alfa in PTPs aged < 12 years with severe HA. It included 74 boys (38 < 6 years and 36 aged 6 to < 12 years) on a weekly prophylaxis regimen with 50 IU/kg efanesoctocog alfa for 52 weeks. No FVIII inhibitors were detected (0%; 95% CI, 0-4.9). The mean half-life was 40.2 hours, with a mean F8 level > 40% for 3 days (vs. 4.1 days in adults and adolescents > 12 years), > 15% for approximately 5 days, and > 10% for approximately 7 days (vs 15.2% in XTEND-1). The median ABR was 0 (IQR, 0-1.02), with a mean ABR of 0.89 (IQR, 0.56-1.42). Most bleeds resolved with a single 50 IU/kg dose, and the response to treatment was excellent or good in 98% of evaluated injections. Perioperative hemostasis was considered excellent in major surgeries performed, without relevant adverse events or treatment discontinuation. It was concluded that the product, in weekly prophylaxis, was well tolerated and provided protection against bleeds and highly effective treatment in children with severe HA, showing high and sustained FVIII activity at normal or near-normal levels (> 40%) for 3 days and around 10% on day 7, above the current trough levels recommended by WFH guidelines[1]. In pharmacokinetics terms, the only parameter that could alter efanesoctocog clearance in children appears to be body weight[12]. Regarding surgical procedures, due to its characteristics, it will allow major procedures without the need for continuous infusion.

Discussion

The XTEND-1 trial results in the ≥ 12 years population are really interesting, demonstrating that weekly infusions of 50 IU/kg of efanesoctocog are associated with trough levels ≥ 15% on day 7. It has long been recognized that joint bleeds would not be expected in patients with a baseline factor level ≥ 15%, with joint bleed reductions to nearly zero[16] when factor levels are > 12%. As reported by Wang et al.[17], the main independent prognostic factor affecting joint mobility in these patients is factor activity, especially in those with levels < 10%. These *a priori* objectives can be met with the concentrate in question. It goes without saying that the main factor affecting the quality of life of hemophilia

patients is the severity of joint deterioration[18], hence the need to emphasize the excellent results and degree of protection observed in the XTEND-1 trial, with 72% of patients without hemarthrosis and 80% without spontaneous bleeds.

The good results reported in the XTEND-1 trial led some authors[19] to conduct an adjusted indirect comparison of treatment with efanesoctocog alfa or emicizumab for bleeding prophylaxis in adults and adolescents with severe HA without inhibitor, using the results of the HAVEN-3 trial[20] on bleeding prophylaxis with emicizumab in PTPs adults and children ≥ 12 years as a reference. In general, it is concluded that prophylaxis with efanesoctocog alfa demonstrated superiority over emicizumab, with significantly reduced rates of any bleeding, treated bleeding, or treated joint bleeding. No significant difference was noted in the rate of treated spontaneous bleeds. An improvement in HJHS (Hemophilia Joint Health Score) score is observed, which is associated with the normal or near-normal F8 levels achieved with efanesoctocog alfa and the larger area under the curve. According to the authors, the higher efficacy and improved pharmacokinetic properties would make efanesoctocog an important addition to the hemophilia therapeutic landscape.

In the ≤ 12 years pediatric population, the results are not far from those reported, for example, for emicizumab, although they are not comparable due to the study design and included population. In 2019, the results of the phase III HOHOEMI trial[21], evaluating weekly (n = 6) or biweekly (n = 7) prophylaxis with emicizumab in pediatric patients, aged 4 months to 10 years, previously on CF VIII concentrates prophylaxis (except the 4-month-old patient), over a 24-week period were presented. Two out of 6 and 5 out of 7 patients did not experience any treated bleeds, and the treated bleed ABRs were 1.3 (95% CI, 0.6-2.9) and 0.7 (95% CI, 0.6-2.9), respectively.

The interim analysis of the AOZORA trial[22] has been recently published. This study includes patients < 12 years with severe HA without inhibitor who had either not previously received emicizumab or participated in the HOHOEMI study[21]. The study is expected to last 6 years from inclusion. The treated and treated joint bleed ABRs are evaluated. At 3 years, there is a reduction in the mean treated bleed ABR after starting emicizumab, from 3.7 (95% CI, 0.94-9.80) down to 0.7 (95% CI, 0.1-5-10); for treated joint bleeds, the ABR decreases from 0.4 (95% CI, 0.00-4.55) down to 0.2 (95% CI, 0-4.04).

The real-life experience reported by the PedNet group[23] included a total of 251 children (median age at treatment initiation: 6.1 years; IQR, 2.1-12), 63% of whom had no anti-FVIII inhibitor. A total of 94% had severe HA, and 76% were < 12 years old at emicizumab treatment initiation. The median follow-up time before emicizumab was 1.51 years and with emicizumab, 1.23 years. During emicizumab prophylaxis, a reduction in the mean ABR from 2.8 down to 1.1 ($p < 0.001$) and joint bleeding from 0.8 down to 0.3 ($p < 0.001$) is observed. Therefore, no significant differences are seen in the reported mean ABR results: 0.89 in XTEND-Kids and 1.1 in PedNet with emicizumab.

Regarding inhibitor development, no FVIII inhibitor antibodies were detected in the efanesoctocog alfa clinical program, even in patients < 12 years in XTEND-Kids[12,14,15]. Transient antibodies against the drug were detected in 2.2% of patients (4/277) during treatment (up to 49.64 weeks) in clinical studies, without impacting FVIII activity-time profiles, pharmacokinetic parameters, bleeding, or pharmacodynamic response[12,14]. In any case, product switching is not considered a risk factor for developing anti-FVIII antibodies[24], and the overall de novo inhibitor incidence in PTPs with HA is as low as 3 per 1000 person-years[25].

For the final efanesoctocog molecule, amino acid sequences with potential to bind to type II major histocompatibility complex (MHC) receptors were modified. The R1680 site (both wild-type and mutated) had potential to bind to MHC, so 9 amino acid residues from the B domain were removed, generating a final molecule with only 5 amino acids from this domain (SFSQN) to reduce the immunogenic risk. Efanesoctocog has endogenous protein domains (D'D3 and Fc) to which people have shown good tolerance and a FVIII sequence, which is similar to other rFVIII products[26]. The XTEN polymers are created as non-immunogenic polypeptides formed by 6 hydrophilic and chemically stable amino acids (A, E, G, P, S, and T). They have been used to extend the half-life of various peptide and protein-based therapies. To date, clinical data suggest that their immunogenicity in humans is very low or null[27].

Regarding the inconvenience of IV product administration, sometimes requiring the placement of an intravascular device like a Port-a-Cath, the weekly regimen could almost completely resolve it, as reported in the literature. A Swedish study[28] concluded that age at prophylaxis initiation was an independent predictive factor for developing arthropathy, being more important than the regimen. Assuming early prophylaxis initiation (before age 2 or before the first hemarthrosis), regimens could be individualized to reduce venous access problems at the start of prophylaxis at a very young

age[29], which is an approach reinforced with the advent of EHL-CF VIII concentrates. The original goal of starting prophylaxis with a weekly infusion was to "train the vein" and avoid the use of an intravascular device. Stepped regimens reduced intravascular device use from 88% down to 27% and achieved better acceptance of CF VIII concentrates prophylaxis, with its associated burden, by both parents and caregivers. In the PedNet publication[30], it is reported that weekly CF VIII concentrates prophylaxis was the most common form of initiation, increasing from 49% of children from 2000 through 2009 up to 68% from 2010 through 2019, and at an earlier age (median, 13.1 vs. 17.6 months). Additionally, FVIII doses were reduced, from a mean of 43.5 IU/kg (IQR, 34.6-49.0) down to 30.9 IU/kg (IQR, 26.3-46.3). After 2010, a total of 60% of severe HA patients started prophylaxis before experiencing any bleeding, except for sporadic cases diagnosed significantly later (median, 8.3 months; IQR, 3.7-11.9) who also had more bleeding before prophylaxis initiation[30]. Weekly prophylaxis is the most common initiation form (68%), and there is a trend to start it at an earlier age (13.1 months). Efanesoctocog will likely facilitate this earlier initiation than reflected in the PedNet publication[30]. Prophylaxis could be complete, weekly, without the need for an intravascular device, improving its tolerability and efficacy. More studies are needed to corroborate this hypothesis, as body weight may alter efanesoctocog alfa clearance in children[12].

For the lack of studies evaluating the safety and efficacy profile in PUP, especially in those < 12 months of age, it is not possible to make indirect comparisons with emicizumab as done in adults. The HAVEN 7 study[31] results on emicizumab prophylaxis safety and efficacy in children < 12 months are very good, with an intracerebral hemorrhage incidence rate of 0 in 56 patients. A 2017 PedNet publication[32] on the incide rate of intracerebral hemorrhages in children and adolescents with severe hemophilia A or B reported that, for children aged 0 to 12 months on complete prophylaxis (i.e., 3 times/week) on CF VIII concentrates, the intracerebral hemorrhage incidence rate was 0, the same as for the partial prophylaxis group, estimating a risk of intracerebral hemorrhage for the former of 0.00033/child-year, almost nil. Efanesoctocog will likely change the concept of complete prophylaxis, *a priori*, to a weekly infusion, and the intracerebral hemorrhage risk will remain the same or even lower. At a time when there is controversy on whether tolerize FVIII[33,34], efanesoctocog could address both issues: tolerization and bleeding protection; moreover, prophylaxis would be "more physiological," replenishing the deficient protein.

Efanesoctocog alfa inaugurates a new class of ultra-long plasma life CF VIII concentrates, bridging the physiological limitation that vWF imposed on extending the plasma half-life of these agents. This, along with the safety and efficacy profile demonstrated in the XTEND clinical trials, suggests that CF VIII concentrates prophylaxis may likely resume its leading role by allowing thrombin generation to be normalized or near-normalized physiologically. More studies are needed to evaluate the safety and efficacy profile in other scenarios, such as PUP, and in preventing intracranial hemorrhage at an early age. However, it represents a therapeutic opportunity and a significant step toward mental and physical liberation from hemophilia and its treatment[35].

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Conflicts of interest

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CLINICAL CASE

First report of renal replacement therapy using hemodialysis in a patient with severe hemophilia B in Uruguay: a clinical challenge

Primer reporte de terapia de reemplazo renal mediante hemodiálisis en paciente con hemofilia B grave en Uruguay: un desafío clínico

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Case presentation

Hemophilia B is an X-linked genetic bleeding disorder that results in a deficiency of coagulation factor IX. It has an estimated incidence of 5 cases per 100,000 male births, being much less frequent than hemophilia A[1].

Advances and greater availability of treatments for hemophilia have increased the life expectancy of these patients, which currently approaches that of the general population[2]. This has led to a parallel increase in age-associated comorbidity, such as cardiovascular diseases, chronic kidney disease (CKD), and cancer[3].

The increasing prevalence of CKD in patients with hemophilia is also associated with various risk factors (Table 1), making a multidisciplinary approach essential for its prevention[4]. In cases of end-stage renal disease, renal replacement therapy (RRT) in patients with hemophilia represents a unique challenge due to their hemorrhagic risk, the scarcity of available standardized clinical practice guidelines, and the complexity in selecting the dialysis modality, vascular access, and administration of clotting factor before or after the procedure.

The objective of this article is to report the first case of a patient with severe hemophilia B and end-stage CKD requiring RRT by hemodialysis in Uruguay. This case offers us the opportunity to discuss the most important aspects related to the management of RRT in patients with hemophilia and to analyze strategies to minimize the development of complications.

A 54-year-old male from Montevideo, with a disadvantaged socioeconomic background, presented with severe hemophilia B (factor IX activity < 1%) without inhibitor. He was on prophylaxis with AIMAFIX (plasma-derived factor IX) at a dose of 40 IU/kg, twice weekly, and had a history of insulin-dependent diabetes mellitus, arterial hypertension, cured hepatitis C, and porphyria cutanea tarda. He had diabetic nephropathy, with stage V CKD according to the KDIGO classification (glomerular filtration rate: 13 ml/min/1.73 m^2).

Coordinated admission for RRT was planned. The patient presented with severe hemophilic arthropathy in

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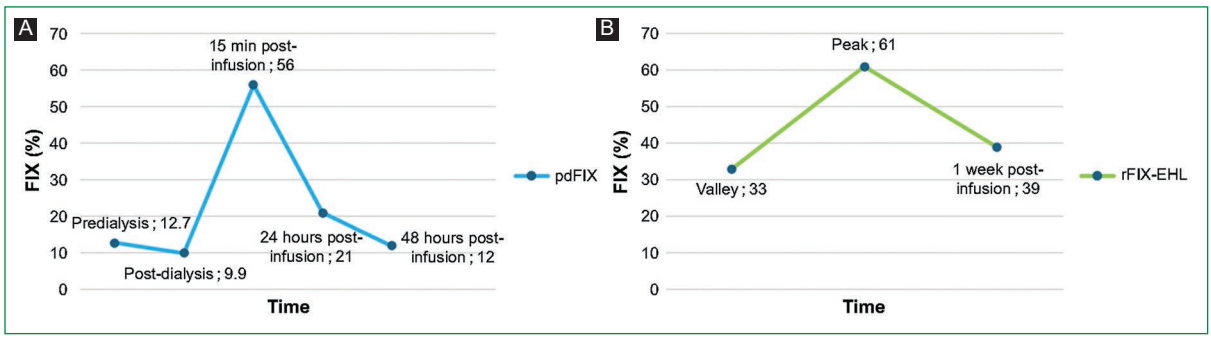

Figure 1. Pharmacokinetics of factor IX. **A:** treatment with plasma-derived factor IX (pdFIX). **B:** treatment with recombinant extended half-life factor IX (rFIX-EHL).

Table 1. Risk factors for developing chronic kidney disease in patients with hemophilia

Risk factor	Mechanism
Age	Loss of renal mass Decreased renal blood flow Decreased glomerular filtration rate Membranous nephropathy
Recurrent hematuria	Obstructive uropathy Anatomical sequelae in the urinary tract
Use of antifibrinolytics	Obstruction by clots (ureters, bladder) Direct nephrotoxic effect
Arterial hypertension	Nephroangiosclerosis
Diabetes mellitus	Diabetic nephropathy
Benign prostatic hyperplasia	Obstructive uropathy
HIV infection	HIV-associated nephropathy Drug-induced nephrotoxicity (ART, antimicrobials) Thrombotic microangiopathy Neoplastic infiltration (lymphoma, Kaposi's sarcoma)
Hepatitis B or C virus infection	Membranoproliferative Glomerulonephritis (immune complex-mediated) Mixed cryoglobulinemia
ITI in hemophilia B with inhibitors	Nephrotic syndrome

ITI: immune tolerance induction; ART: antiretroviral therapy; HIV: human immunodeficiency virus.

the elbows that limited the range of motion and manual dexterity, hindering the implementation of peritoneal dialysis. Following multidisciplinary evaluation (hemotherapy, nephrology, and vascular surgery), hemodialysis via a tunneled jugular venous catheter was chosen, avoiding the use of an arteriovenous fistula due to the risk of post-puncture hematomas.

Hemodialysis sessions were established three times a week, without using heparin, and plasma-derived factor IX was administered after dialysis (dose of 60 IU/kg). The pharmacokinetics of factor IX (Fig. 1) were analyzed using a one-stage coagulation assay based on activated partial thromboplastin time (aPTT), obtaining blood samples pre- and post-dialysis, and at 15 minutes, 24 and 48 hours after factor IX infusion. A trough level of factor IX pre-dialysis of 12.7% was observed, without significant variations compared to post-dialysis values, with a total session duration of 4 hours. After 3 months, albutrepenonacog alfa (extended half-life recombinant factor IX) was initiated as prophylaxis, at a dose of 40 IU/kg per week, maintaining trough factor IX levels at 33% (Fig. 1). Currently, after 15 months on hemodialysis, the patient has not experienced any bleeding related to the procedure.

Discussion

We report a case of hemophilia B and end-stage CKD that safely initiated RRT by hemodialysis with prophylactic factor IX replacement. This case illustrates the challenges of managing renal replacement therapy in patients with hemophilia.

As the life expectancy of patients with hemophilia increases, the frequency of cases of end-stage CKD requiring RRT also rises, necessitating careful selection of the safest and most effective dialysis modality. There is no general consensus to guide decision-making; therefore, the evidence derives primarily from case reports and expert opinions.

Peritoneal dialysis is often preferred in patients with hemophilia, as the risk of bleeding is lower compared

with hemodialysis[5,6]. Administration of coagulation factors is usually required only at the time of catheter placement, and episodes of hemoperitoneum are infrequent[5,6]. However, there is a greater risk of peritonitis and, in some cases, reduced efficacy in the clearance of small solutes[5,6]. This modality was ruled out in our patient due to his disabling arthropathy, as motor limitation precluded self-administration of peritoneal exchanges.

Hemodialysis is considered a higher risk due to repeated vascular punctures, although more evidence is needed in this regard. The use of arteriovenous fistulas or permanent catheters is possible, but requires strict monitoring to prevent bleeding[7-10]. As demonstrated in this case, hemodialysis through a tunneled central venous catheter can be performed safely with appropriate strategies for coagulation factor replacement and limitation of anticoagulant use. The choice of a tunneled catheter prioritized safety aspects; however, long-term use of this type of device predisposes to the development of catheter-related infections.

Patients with hemophilia B require replacement therapy with coagulation factor IX when undergoing invasive or surgical procedures. Most dialysis membranes have pores that prevent the passage of albumin (69 kDa), and consequently, factor IX, with a lower molecular weight (55 kDa), could be removed during dialysis, making its administration necessary after each hemodialysis session[8]. This therapeutic strategy was safe and effective in the analyzed case, reinforced by the pharmacokinetic analysis, which demonstrated minimal intradialytic clearance of factor IX.

It is important to emphasize that trough factor IX levels above 10% were sufficient to prevent bleeding, validating the suggested minimum protocols[4]. The omission of systemic heparin use further contributed to reducing the risk of hemorrhagic complications, without thrombus formation in the extracorporeal circuit. The successful transition to extended half-life recombinant factor IX therapy allowed for higher trough factor IX levels, while reducing the infusion burden.

Finally, although CKD can generate platelet dysfunction secondary to uremia and potentially increase hemorrhagic risk, this is usually corrected with dialysis[4]. It has been observed that platelets tend to adhere to the artificial surfaces of dialysis membranes; therefore, periodic platelet count monitoring is recommended in patients with hemophilia on dialysis if increased bleeding is identified[4].

Conclusions

The increase in life expectancy of patients with hemophilia is expected to lead to a rise in the prevalence of comorbidities, such as CKD. It is urgent and important to deepen the therapeutic approach for patients with hemophilia and end-stage renal disease, given the limited quality evidence currently available. The present case, the first reported in Uruguay, demonstrates that hemodialysis is a viable and safe method in patients with severe hemophilia B through a multidisciplinary approach focused on: 1) vascular access via long-term tunneled catheter to reduce hemorrhagic risk, 2) omission of systemic heparin, combined with post-dialysis administration of factor IX concentrate, and 3) serial pharmacokinetic monitoring for dose optimization. The stability of post-dialysis plasma factor IX levels supports that its high molecular weight significantly limits its clearance by the procedure.

Given the progressive aging of this population, it is imperative to develop standardized clinical practice guidelines that integrate the use of extended half-life factor IX concentrates and personalized management protocols for patients requiring RRT. This experience provides practical evidence for the management of this complex clinical scenario, whose prevalence will increase in the coming decades.

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Conflicts of interest

None.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, have obtained informed consent from the patient, and have received approval from the Ethics Committee. The recommendations of the SAGER guidelines have been followed, according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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LETTER TO THE EDITOR

Celebrating half a century of collaboration in hemostasis and thrombosis: the first 50 years of the Latin American Cooperative Group on Hemostasis and Thrombosis (CLAHT Group)

Celebrando medio siglo de colaboración en hemostasia y trombosis: los primeros 50 años del Grupo Cooperativo Latinoamericano de Hemostasia y Trombosis (Grupo CLAHT)

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Dear Editor,

On behalf of the Latin American Cooperative Group on Hemostasis and Thrombosis (CLAHT), we write to you on the occasion of a momentous milestone: the first 50 years of our organization.

Our roots trace back to the First Latin American Conference on Cooperative Work in Hematology, held in Havana, Cuba, from February 18 to 21, 1973. This event, sponsored by the Pan American Health Organization, the Inter-American Division of the International Society of Hematology, and the Ministry of Public Health of Cuba, laid the foundation for unprecedented collaboration in the region. The initial objective was to connect working groups in hemostasis and thrombosis throughout Latin America, with the mission of elevating the level of knowledge and fostering cooperative research.

CLAHT forged its foundations in Mexico City in 1975 during a key organizational assembly guided by the leadership of Dr. Javier Pizzutto, its first coordinator. This initiative was formally consolidated the following year with its official establishment at the Caracas meeting in 1976. Among its distinguished founding members are Drs. Raúl Altman, Adela Martínez-Canaver, Eduardo Sack, Miguel Pavlovsky, Celso de Campos Guerra, Jorge Maldonado, Delfina Almagro, Samuel Dorantes Mesa, Javier Pizzuto Chávez, Carmen Luisa Arocha-Piñango, Carlos Goldstein, Francisco Ruiz, José Luis Pérez Requejo, and Tulio Arends. Since that milestone, CLAHT has expanded its influence, currently bringing together experts from 16 countries with approximately 400 members, and has established essential working committees that address critical areas such as hemophilia, von Willebrand disease, thrombophilia, and antithrombotic therapy, demonstrating its vital role in advancing the field of hemostasis and thrombosis in the region.

During these 50 years, CLAHT has served as a fundamental pillar for research, education, and clinical practice. The fellowship and solidarity we have cultivated have enabled the creation of data registries, the implementation of clinical guidelines adapted to our reality, and the support for specialist training through

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fellowships at the various CLAHT reference centers. Our strength lies in our ability to connect professionals from diverse contexts through biennial congresses that promote knowledge and innovation, and more recently through online web seminars and traveling symposia sponsored by CLAHT in different member countries. These activities have further enriched our network, ensuring continuous and accessible education for all.

As we look to the future, our commitment to global cooperation is stronger than ever. This anniversary is a moment to reflect on our journey and reaffirm our dedication to working alongside scientific societies around the world. Only through such collaboration can we address the challenges that still persist, such as equity in access to healthcare and research on the most complex pathologies.

We thank the *Revista Iberoamericana de Hemostasia y Trombosis* for being a key platform for disseminating scientific knowledge in our field, and we hope to continue sharing with you the fruits of our work.

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None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CORRIGENDUM

Corrigendum in the article by D.C. Castillo-González et al. Implementation of a work system for the introduction of emicizumab in Cuba

Corrigendum en el artículo de D.C. Castillo-González et al. Implementación de un sistema de trabajo para la introducción del emicizumab en Cuba

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The authors of the published version of the article "Implementación de un sistema de trabajo para la introducción del emicizumab en Cuba" published in Hemost Trombos. 2025;2(3):109-113 (DOI: 10.24875/RHT.24000015), wish to indicate that Table 1 contained errors in the numerical data.

Below is the corrected version of the table, which replaces the one originally published.
These corrections do not affect the conclusions of the article.

Table 1. Patients proposed at initiation and currently treated with Hemcibra®

Indication	Patients					
	Pediatric		Adult		Total	
	Proposed	Treated	Proposed	Treated	Proposed	Treated
Hemophilia A with inhibitors	7	4	14	9	21	13
Hemophilia A without inhibitors	23	40*	17	5	40	45
Total	30	44†	31	14	61	58

*Includes 12 infants not initially considered, one patient who developed inhibitors during this stage, and four patients who presented life-threatening bleeding manifestations.

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