

## Clinical decision-making beyond the threshold of classification in bleeding coagulation disorders

### La decisión clínica más allá del umbral de la clasificación en las coagulopatías hemorrágicas

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In the classical view, medicine requires classification to understand and make decisions. Thus, we speak of severe, moderate, or mild hemophilia; congenital or acquired diseases; plasma-derived or recombinant products; and response, failure, or remission. This nomenclature enables us to organize knowledge, compare outcomes, and develop recommendations. However, no classification fully encompasses reality or anticipates the scenarios that may arise during the course of a disease. A classification is only a starting point: 2 patients assigned the same label may follow profoundly different clinical trajectories and have markedly different needs and risks.

This issue of *Hemostasia y Trombosis: Revista Latinoamericana de Trombosis y Hemostasia* focuses on bleeding disorders, particularly hemophilia, at a time when the emergence of promising therapeutic alternatives has clearly broadened the options available for clinical decision-making. When few options existed, the diagnostic category led almost directly to the treatment that should be prescribed. Currently, with concentrates possessing different properties, and rebalancing therapies, new indications for prophylaxis, and the introduction of gene therapy, disease classification

continues to guide us, but it is no longer sufficient. Beyond this threshold, other variables become increasingly important, including bleeding phenotype, disease trajectory, comorbidities, pharmacokinetics, age and general health status, immunologic risk, and patient preferences.

The experience of the first patient treated in Spain with etranacogene dezaparvovec exemplifies this change. A diagnosis of severe hemophilia B makes it possible to identify potential candidates, but it does not determine, *per se*, who should receive gene therapy. In the case presented in this issue,<sup>1</sup> the therapy made it possible to discontinue prophylaxis and achieve factor IX activity close to 50% at 3 months, with no further bleeding episodes. Nevertheless, the elevation in transaminase levels and the need for corticosteroid therapy demonstrate that the outcome cannot be summarized solely by a factor level. Experience with gene therapy in hemophilia B shows that meeting regulatory criteria is not enough. Candidate selection must take into consideration the patient's liver status, ability to adhere to demanding follow-up, and expectations. Patient motivation, hepatic and psychological assessment, and the center's capacity to provide close

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follow-up are fundamental components of treatment understood as comprehensive medical care.

This issue of the journal also leads us to a more traditional question: who needs prophylaxis? The study by Rodríguez-Esteban et al.<sup>2</sup> shows that the distinction between severe, moderate, and mild hemophilia based solely on baseline factor activity does not always reflect the severity of the clinical condition and, consequently, the need for prophylaxis. Severity defined according to baseline factor level may underestimate the true burden of disease, and additional assessment of bleeding history, joint damage, physical activity, and quality of life may justify a more intensive preventive strategy. A patient may be classified as “moderate” on the basis of laboratory findings yet experience a clinical burden that warrants a preventive strategy characteristic of “severe” disease. In a series of patients with nonsevere forms of hemophilia, prophylaxis reduced the annualized bleeding rate by more than 90% and virtually eliminated emergency visits for bleeding. In this setting, the factor level did not change, but the interpretation of its significance did. Hemarthroses, pain, joint damage, physical activity, and dependence on hospital care place some patients beyond what may be indicated by a classification based solely on laboratory data.

Classification processes may inadequately describe changes and intercurrent events arising in clinical practice. This is illustrated by the case reported in this issue of a young patient with mild hemophilia A who developed a high-titer inhibitor after intensive exposure to factor VIII.<sup>3</sup> A disease managed for years as mild therefore abruptly acquired a much more complex bleeding phenotype, demonstrating that an initially favorable category is not immutable. The case reminds us that “mild” describes a level of factor activity but does not eliminate risks, such as immunologic risk, which may persist throughout life. In these cases, therapeutic decisions must also integrate bleeding severity, the risk of recurrence, and treatment toxicity.

Moreover, the increasing life expectancy of people with hemophilia requires decisions in areas for which traditional classifications provide few answers. Prasca et al.<sup>4</sup> describe the endovascular treatment of an intracranial aneurysm in a patient with severe hemophilia A who required dual antiplatelet therapy. The difficulty lay not in identifying or classifying the 2 diseases, but in making their treatments compatible. In the absence of specific recommendations, individual pharmacokinetic data were used to maintain adequate factor VIII trough levels during the period of greatest risk. This case demonstrates that the hemostatic target must be

adjusted to the concomitant risk and modified whenever that risk changes.

Another example of a delicate balance is found in the patient described with acquired hemophilia A.<sup>5</sup> The 90-year-old patient had colorectal cancer, postoperative bleeding, and a high-titer inhibitor, simultaneously combining frailty, bleeding risk, and thrombotic risk. The decision did not involve choosing between hemostasis and inhibitor eradication, but rather separating the 2 objectives over time. Emicizumab created a window of protection, although this advantage must be balanced against thrombotic risk, cost, and the absence of an approved indication in most countries.

Furthermore, classification affects therapeutic products. The term von Willebrand factor concentrates encompasses preparations with different compositions, different ratios of von Willebrand factor to factor VIII, and different pharmacokinetic profiles. The article by Salvado et al.<sup>6</sup> analyzes how these differences may influence thrombin generation, factor VIII accumulation, and thrombotic risk. Although indirect comparisons require caution, the study shows that selecting a concentrate does not simply involve replacing a given amount of protein. It is also important to assess how its components interact, when they reach peak levels, and how they behave after repeated exposure. The name identifies the product, but its pharmacology helps determine how it should be used.

A similar consideration applies to viral safety. The term “plasma-derived” inevitably retains the memory of infections transmitted during the last century. However, the review published in this issue<sup>7</sup> shows that the origin of a product cannot be used as a substitute for a genuine risk assessment. Donor selection, molecular screening, purification, and successive viral inactivation or removal steps have made it possible to achieve unprecedented levels of safety. The importance of sustained pharmacovigilance must be emphasized. The absence of confirmed transmissions in modern series does not mean that surveillance is unnecessary; rather, it is precisely the result of maintaining such surveillance. Safety does not reside in a label, but in the robustness of the process underlying it.

Finally, the study of avatrombopag in immune thrombocytopenia extends this same reflection.<sup>8</sup> The efficacy of a thrombopoietin receptor agonist could be classified according to the platelet count response, but this measure does not fully reflect its clinical value. In the 22 patients analyzed, avatrombopag produced a sustained increase in platelet count, enabled a reduction in concomitant treatments, and decreased the mean

weekly cost per patient by approximately 62%. Although the limitations of a single-center series require the magnitude of the economic effect to be interpreted cautiously, resource use is also part of clinical decision-making. A treatment does not fully achieve its objective when its benefit is difficult to sustain for either the patient or the healthcare system.

The studies gathered in this issue do not question the need for or usefulness of classification. Classification remains the language through which we recognize disease, conduct research, and build shared knowledge. What these studies demonstrate is that clinical medicine must adapt when reality extends beyond that initial description. The threshold is therefore not the point at which classification loses its value, but the point at which it ceases to be sufficient. Before that threshold is crossed, the category provides guidance and indicates the path forward; beyond it, biology, disease course, and context must guide the decision.

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