

## Preface

# Alloantibodies and Congenital Bleeding Disorders: New Insights in the Pathogenesis and Management

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The hemophilia community is living in exciting times, thanks to recent and relevant developments in this field and great expectations for new treatment approaches that are able to significantly and positively affect patients' outcomes and quality of life.<sup>1–5</sup> Interestingly, one most important innovation, a hemostatic agent enabling a very effective prophylaxis of bleeding given subcutaneously (the bispecific antibody against factor [F] X and activated FIX emicizumab),<sup>2,3</sup> is being introduced for patients who developed alloantibodies against FVIII, the so-called inhibitors. The management of these patients has always been considered challenging because inhibitors make the standard effective and safe replacement with FVIII concentrates unfeasible and, therefore, make difficult the treatment of bleeding, leaving patients at a high risk of complications, both in the acute phase and in regard to long-term morbidity.<sup>6</sup> Due to the epidemiological impact of inhibitors (present in ~30% of previously FVIII-unexposed patients and persistent/high titer in two-thirds of cases),<sup>6,7</sup> searching for pathophysiological mechanisms and strategies for management is particularly important in hemophilia A (HA). Indeed, a relevant body of literature addressing such issues has been generated over the last decades. However, significant challenges are also raised by the inhibitors encountered, albeit less frequently, in clinical practice in other congenital bleeding disorders (CBDs): (1) in hemophilia B (HB) and von Willebrand's disease (VWD), additional morbidity due to allergic reactions can occur;<sup>6,8</sup> (2) in rare CBDs, little information concerning management is available;<sup>9</sup> and (3) in deficiencies of platelet membrane glycoproteins, the clinical impact of alloantibodies and alternative treatment approaches are poorly understood.<sup>10</sup> With this background, the 11 chapters presented in this latest issue of *Seminars in Thrombosis and*

*Hemostasis* deal with the current state of the art of pathophysiology and management of alloantibodies in CBDs. It is easy to understand why seven of them focus on hemophilia, particularly on HA, discussing, at this current time of possible evolving scenarios, the most recent literature data. Alloantibodies in HB, VWD, rare CBDs, and congenital deficiencies of platelet surface glycoproteins are reviewed in the remaining four chapters.

Three chapters focus on novel approaches to gain insight into molecular mechanisms of inhibitor development in hemophilia. In this respect, the role of genetic factors, particularly of the causative mutation type, and their complex interaction with nongenetic risk factors are well established, with extensive studies in HA.<sup>11,12</sup> Margaglione and Intrieri therefore briefly review available evidence concerning both genetic, nonmodifiable and potentially modifiable risk factors, highlighting the so far unanswered need for clinical scoring systems to predict and quantify the inhibitor risk in each patient.<sup>13</sup> These authors also report how complex and multifactorial phenomena, such as inhibitor development, are currently being addressed by the "omics" technologies, that is, the holistic approaches developed for studying biomolecules such as DNA, RNA, and proteins when, in the lack of a definite or proposed hypothesis, all data are acquired and analyzed to generate hypotheses. Thus, genome-wide expression studies investigate the activity of the genome rather than inherent genome variations and may identify which genes (and to what extent) are "switched on" in any given situation, such as when inhibitors develop. These studies may enable a more accurate estimation of the personal risk profile, even at periodic assessment, to draw information to predict and, perhaps, prevent inhibitor formation.<sup>13</sup>

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The increasingly acknowledged pivotal role of the modulation of immune response in inhibitor generation is addressed in the next article by Delignat et al.<sup>14</sup> These authors summarize the latest findings regarding the molecular interactions leading to the recognition of FVIII by the immune cells and to the possible outcomes of such interactions, that is, T-cell activation or tolerance induction, the validity of the proposed risk factors for FVIII alloimmunization in the light of the danger signal theory, and the possible therapeutic approaches to prevent or control the anti-FVIII immune response. These strategies, evaluated in preclinical models of HA, are aimed to prevent HLA-DR (human leukocyte antigen - antigen D related) mediated interactions between antigen-presenting cells and T cells, or to inhibit B cells, or to induce T-cell specific tolerance.<sup>14</sup>

Searching for therapeutic approaches able to prevent or eradicate inhibitors is not exclusive of hemophilia. Hassan et al report an interesting overview of alloantibody prevention or eradication strategies used in other diseases in the attempt of drawing lessons for HA.<sup>15</sup> In patients with Pompe's disease, the possibility of effectively preventing inhibitors with rituximab, methotrexate, and intravenous immunoglobulins is, however, associated with a high risk of adverse events. In patients with rheumatoid arthritis and inflammatory bowel disease, treatment with methotrexate alone is likely to be able to prevent inhibitors. However, besides side effects, it is unclear whether such prevention persists after cessation of immunomodulatory therapy with methotrexate. A combination of cyclophosphamide and corticosteroids, used to treat antibody-mediated pure red cell aplasia, could be taken into consideration to eradicate inhibitors in HA patients who are refractory to immune tolerance induction (ITI).<sup>15</sup> Overall, the transferability of these concepts to HA should be carefully investigated.

Two further chapters deal with the management of bleeding in hemophilic patients with inhibitors, currently based on bypassing agents (activated prothrombin complex concentrate and recombinant activated FVII).<sup>16</sup> As reported by Barg et al,<sup>17</sup> treatment of bleeding should be tailored according to the characteristics and response of each patient, taking into account that no validated assay is currently available to predict the risk of bleeding or the response to treatment, monitoring its efficacy and safety. These authors report their institutional approach for individual therapy tailoring, including the use of global hemostatic assays, increasingly used to assess coagulation status in this setting and potentially useful even for the emerging nonreplacement therapies.<sup>17</sup> Consistent with the search for individualized treatment, the survey performed by the Italian Association of Hemophilia Centers, reported by Coppola et al,<sup>18</sup> describes the treatment regimens with bypassing agents adopted in inhibitor patients and criteria for clinical choices.<sup>18</sup> Interestingly, to avoid severe, recurrent, and/or difficult-to-treat bleeding, prophylactic regimens with both bypassing agents are used in almost 40% of patients. These regimens are quite heterogeneous, with adjustment of doses and frequency of administration to optimize clinical outcomes, mainly in younger patients.<sup>18</sup>

Due to the huge impact of inhibitor development on costs of treatment, pharmacoeconomic analyses are crucial in this setting but remain controversial. As reviewed in the article by Messori,<sup>19</sup> relevant issues include treatment in high-titer versus low-titer inhibitors, influence of FVIII products on inhibitor risk, effectiveness of different ITI regimens, different types and regimens of bypassing agents, and, presently, the development of new nonreplacement approaches. In particular, data on cost-effectiveness of ITI are not conclusive; however, the high investment of inhibitor eradication seems to be offset in the long term by the subsequent savings in the cost per patient. Interestingly, even from the pharmacoeconomic perspective, novel treatments (i.e., emicizumab) are likely to deserve substantial advantages in patients with inhibitors.<sup>19</sup>

The last chapter concerning alloantibodies in HA deals with those arising in patients with nonsevere HA. Recent data indicate that at variance with severe HA, inhibitor development in this setting shows a lifelong risk but is similarly associated with a deterioration of clinical outcomes, with increased bleeding and mortality rates.<sup>20,21</sup> Abdi et al review available data on risk factors for inhibitors in nonsevere HA, including specific F8 missense mutations as well intensive treatment, for example, on the occasion of surgical interventions or severe bleeding treated with high doses of FVIII concentrate. Even in this setting, adequate prevention and treatment of inhibitors is limited by the poor knowledge of the underlying immunological mechanisms required to identify high-risk patients, to understand the association between clinical risk factors and inhibitor occurrence, and to provide the opportunity to develop new preventive and therapeutic strategies.<sup>22</sup>

The development of inhibitors against FIX is less frequent in HB (1.5–3% of all patients) than in HA and occur almost exclusively in severe patients and in tight association with specific F9 genotypes.<sup>23</sup> However, rigorous epidemiological studies of incidence are lacking, and recent analyses in the highest-risk population of previously unexposed patients with severe disease suggest that inhibitor rates are higher than previously reported.<sup>24</sup> In spite of comparative rarity, inhibitor development in HB is associated with a relevant morbidity not only due to the bleeding risk but particularly due to the occurrence of allergic/anaphylactic reactions after FIX concentrate exposure. These issues are comprehensively reviewed by Santoro et al,<sup>25</sup> who report the data available on risk factors, pathophysiology, and clinical aspects of inhibitors in HB, focusing on the challenging management in patients with a history of allergy or anaphylaxis. Indeed, ITI is often unsuccessful and can be affected by complications such as nephrotic syndrome. For these reasons, alternative therapeutic strategies, now in development, are highly needed.<sup>25</sup>

Similar low frequency and possible serious complications are reported for alloantibody development in VWD. Franchini and Mannucci review the few available data on such complications,<sup>26</sup> described almost exclusively in type 3 VWD, again with higher risk in patients carrying severe gene abnormalities (complete or partial deletions). Beyond

difficult-to-treat bleeding, the management in some cases is even more challenging because anti-von Willebrand factor (VWF) alloantibodies, particularly when in high titer, may precipitate VWF with immune complex-mediated activation of the complement system and be responsible for life-threatening anaphylactic reactions following reexposure to VWF.<sup>26</sup> Overall, the rarity of alloantibody development in CBDs other than HA hampers collection of adequate information about risk factors, clinical aspects, and management. This limitation particularly applies to inhibitors anecdotally reported in rarer CBDs, that is, FV, FVII, FXI, and FXIII deficiencies. The available data for these are described by Franchini et al,<sup>27</sup> who highlight that incidence of inhibitors is unknown or underestimated, risk factors are not elucidated (an association with specific gene mutations has been shown only in FXI deficiency), and management is typically driven by clinical experience, often extrapolated from patients with hemophilia and inhibitors. These authors, therefore, welcome the implementation of collaborative international collection of data in this setting to improve knowledge and management of these cases.

The last chapter of this issue by Poon and d'Oiron<sup>28</sup> deals with alloantibodies arising in patients with deficiencies of platelet membrane glycoproteins following platelet transfusions. These antibodies are directed against HLA antigens and/or the missing glycoprotein(s) (GPs), with anti- $\alpha$ IIb $\beta$ 3 and anti-GPIb-IX in Glanzmann thrombasthenia and Bernard-Soulier's syndrome, respectively, being the most studied clinical settings. Circulating alloantibodies may render future platelet transfusion ineffective, causing platelet refractoriness. Moreover, anti- $\alpha$ IIb $\beta$ 3 and anti-GPIb-IX may cross the placenta during pregnancy and cause thrombocytopenia and bleeding in the fetus/neonate. The authors review a series of unresolved issues of platelet antibodies, i.e., poor knowledge of risk factors for their development, inadequate standardization of diagnostic assays that are not widely available, and lack of clear relationship between platelet antibodies and platelet refractoriness in clinical practice. However, an alternative therapeutic agent to platelet transfusion, recombinant FVIIa, has been shown to be helpful in the management of patients with platelet disorders, particularly those with platelet antibodies and/or platelet refractoriness.

In conclusion, the excellent contributions published in this issue clearly depict the current scenario of alloantibodies in CBDs, with many pathophysiological, clinical, and therapeutic shadows faced by clinicians and researchers. Despite these uncertainties, newer, relevant lights are now expected to cast the shadows aside, for the first time in the history, earlier in inhibitor than in noninhibitor patients.

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