Role of Bispecific Antibody in Hemophilia

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Bispecific antibodies (bsAbs) have entered various medical fields over the past decade, including hematology, oncology, chronic inflammatory disorders, and autoimmune diseases. These biomolecules are designed to simultaneously bind two antigens or epitopes, either on the same antigen or on different ones, and represent innovative targeting solutions for many conditions. It is estimated that more than 200 such molecules are currently in preclinical or clinical evaluation.

The first bispecific antibodies were described over 60 years ago, but they only began to be used in clinical settings at the beginning of the 21st century. Advances in design and manufacturing over the past 20 years have made these compounds more stable, easier to produce, less immunogenic, and capable of persisting longer in circulation. However, the discovery of new bsAbs is driven by the underlying biology, which must be matched with an optimal bsAb design to select the right format, affinity range, and epitopes.

In the hemostasis field, researchers designed, screened, identified, and ultimately manufactured a bispecific monoclonal antibody capable of partially replacing the procoagulant function of factor VIII (FVIII) in the coagulation process. The hypothesis was that a bispecific antibody could have binding sites that recognize and physically connect factor IXa and factor X—a process normally mediated by factor VIIIa. Extensive screening of a large set of bsAbs was required to identify those combining suitable epitopes with optimized affinities and geometry to serve as functional FVIIIa mimetics (1). These mimetics connect the serine protease and its substrate at the phospholipid surface, thereby mimicking the assembly activity of natural FVIII in the clotting process. Preclinical studies demonstrated that coagulation of FVIII-deficient plasma could be improved, with a corresponding shortening of coagulation parameters. Additional biochemical characterization in vitro and in animal models further reinforced these findings (2). This represented not only a remarkable scientific achievement but also a potential solution for effective prophylactic therapy in people with hemophilia who have developed anti-FVIII alloantibodies (PWHI), since the activity of the therapeutic molecule is not affected by anti-FVIII inhibitors due to the lack of homology between the sequences of emicizumab and FVIII. An international phase 3 clinical trial confirmed the efficacy of subcutaneous emicizumab injections and a favorable benefit/risk ratio in PWHI (3). Further clinical development demonstrated that the drug was also efficacious and safe in children with inhibitors (4), as well as in adolescent and adult patients with severe and moderate hemophilia A without inhibitors (5–6). More recently, emicizumab has proven safe and effective in infants, including previously untreated patients with severe hemophilia A and in acquired hemophilia A (7,8). Its subcutaneous administration, flexible dosing intervals, favorable benefit/risk profile, and pharmacokinetic/pharmacodynamic properties have made this drug a major success in the hemophilia treatment landscape. However, while plasma concentrations of emicizumab can be accurately measured, clinical equivalence to FVIII activity remains debated and should be interpreted cautiously with current methodologies (9).

Emicizumab was the first bispecific antibody developed with biological activity roughly equivalent to one-tenth of wild-type FVIII. Recent developments have introduced next-generation FVIIIa-mimetic candidates with the same mechanism of action but with modified binding affinity for their target proteins that affect their FVIIIa-like function (10,11). These candidates are currently under clinical evaluation and are likely to reach the market in the coming years. Nonclinical investigations suggest an improved capacity to promote hemostasis compared to emicizumab. However, their biological activity should be compared to FVIII with extreme caution, as enhanced or even normalized thrombin generation does not necessarily correspond to a normal coagulation profile. In this regard, final data from the clinical development of these new FVIIIa mimetics in people with hemophilia with and without inhibitors will be of particular interest.

The clinical management of hemophilia A has undergone major advances over the past decade. Among the various innovations, the introduction of non-factor therapies has dramatically transformed the treatment landscape, which was previously dominated by factor VIII replacement therapy. Nevertheless, it is important to remember that these non-factor therapies are not biologically equivalent to FVIII, and the concept of “FVIII equivalence” should therefore be used with caution.

References

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