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## **Towards novel treatment options in von Willebrand disease**

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## **Abstract**

Deficiency or dysfunction of von Willebrand factor (VWF) is associated with a bleeding disorder known as von Willebrand disease (VWD). The clinical manifestations of VWD are heterogeneous, and are in part dictated by the structural or functional defects of VWF. The tools to control bleeding in VWD are dominated by VWF concentrates, desmopressin and anti-fibrinolytic therapy. In view of these treatments being considered as effective, it is surprising that quality-of-life studies consistently demonstrate a significant mental and physical burden in VWD patients, particularly in women. Apparently, the current weaponry to support the management of VWD is insufficient to fully address the needs of the patients. It is important therefore to continue to search for innovative treatment options which could better serve the VWD patients. In this short review, two of such options are discussed in more detail: emicizumab to correct for the deficiency of factor VIII, and the pegylated aptamer BT200 to increase endogenous levels of the VWF/factor VIII complex.

**Keywords:** von Willebrand disease, treatment, quality-of-life, bispecific antibody, aptamer

### **Von Willebrand disease (VWD)**

VWF is a multimeric plasma protein that plays an essential role in hemostasis, which is illustrated by the fact that its deficiency or dysfunction coincides with a severe bleeding disorder known as von Willebrand disease (VWD).<sup>1</sup> VWD distinguishes three different types: VWD-type 1 is characterized by reduced levels of a functionally normal VWF protein. VWD-type 2 refers to qualitative defects, with several subtypes according to the patients' functional defect. Finally, VWD-type 3 is manifested by severely reduced (<5%) circulating levels of VWF.

Hemostatic activities of VWF involve the recruitment of platelets to the growing thrombus at sites of vascular injury, as well as the protection of coagulation factor VIII (FVIII) against proteolytic degradation and premature clearance.<sup>2</sup> Indeed, the absence of VWF antigen (as in VWD-type 3) is associated with markedly reduced levels of FVIII, resulting in a combined deficiency of VWF and FVIII. VWD-type 3 patients display a mixed bleeding phenotype, provoked by both defective platelet recruitment and impaired coagulation, and share some of the bleeding symptoms found in hemophilia patients. It is not surprising therefore, that upon the recognition of this complex bleeding disorder by Dr. von Willebrand, it was originally described as hereditary pseudo-hemophilia.<sup>3,4</sup>

### **Treatment options in VWD and hemophilia A**

The interconnection between VWD and hemophilia A is also apparent from the overlap in treatment options, particularly in the period 1960-1980, when first cryoprecipitate and later on intermediate-purity concentrates containing both FVIII and VWF were used as replacement therapy for both hemophilia A and VWD.<sup>5</sup> However, a divergent path in treatment options developed since then. High purity FVIII concentrates (*ie.* poor in VWF content) were developed in the 1980s to serve hemophilia A patients and recombinant FVIII products became available in the 1990s. Additional developments allowed for the introduction of extended half-life variants of FVIII (pegylated-FVIII and FVIII-Fc fusion proteins) in the 2010s and more recently non-factor therapies have been approved (emicizumab) or are in advanced clinical development (fitusiran, concizumab, marstacimab).<sup>6</sup> Finally, gene therapy for

hemophilia A has undergone a rapid development over the last decade, and it seems conceivable that this approach may find regulatory approval within the next couple of years.

In contrast, fewer advances in the therapeutic management of VWD have been made over the last three decades: the introduction of a plasma-derived, FVIII-poor VWF concentrate in 2005 and of a recombinant VWF concentrate, approved in 2015 in the US and in 2017 in Europe.<sup>7,8</sup> This raises the question as to why there is such a disparity between the development of novel therapeutic options in VWD compared to hemophilia A?

### **Why needing better treatment options for VWD?**

The lack of developments with regard to VWD could potentially be ascribed to the absence of a need for such new therapeutics. Indeed, Dr. Mannucci recently expressed that “the weapons currently available for the clinician to manage patients with VWD are satisfactory”.<sup>9</sup> It seems conceivable that when one assumes such a perspective, there would indeed be little incentive to look for new or improved therapeutic strategies.

But is it actually true that the current arsenal of treatment options is satisfactory? One possibility to address this question is to analyze studies that have assessed the quality-of-life situation of VWD patients. These studies consistently teach us that severe and moderate VWD patients have clinically and statistically significant reductions in nearly all health related quality-of-life domains, both physically and mentally (reviewed in Denis *et al.*).<sup>10</sup> These results have not changed over the last 25 years.<sup>11-13</sup> In particular, women express considerable morbidity in emotion and pain. Dr. Kouides stated that “VWD on clinical grounds is primarily a diseases of women”.<sup>14</sup> Indeed, VWD in women is frequently manifested in associated with heavy menstrual bleeding and its associated pain (observed in 32-100% of patients), postpartum hemorrhage (15-60% of patients) and hysterectomy (10-26% of patients).<sup>15-</sup>

So yes, existing treatment options can be effective, but they do not seem to fulfil the need of the patients. We should therefore try to improve therapeutic approaches with the aim to achieve superior efficacy and ameliorate the quality-of-life situation of these patients.

### **Challenges in developing novel treatment options for VWD**

What options do we have to improve the clinical management of VWD? First, prophylactic treatment in VWD is less frequent compared to hemophilia A. This may originate from the perception that bleeding symptoms are commonly believed to be less serious than hemophilia-related symptoms.<sup>20</sup> Nevertheless, the initiation of prophylaxis for VWD patients was found to significantly reduce the rate of bleeding episodes and the need for hospitalization.<sup>21,22</sup> Thus, more frequent application of prophylaxis would already be a step forward. In this respect, the development of extended half-life variants would be welcome. This would be feasible from a technical point of view, given two preliminary studies describing such molecules that were published in 2006 and 2013, respectively.<sup>23,24</sup> It is unclear why no clinical evaluation of these molecules has been initiated.

Another approach would be to focus more on the specific defect of the molecule (such as reduced synthesis, reduced multimerization, increased degradation, impaired platelet binding, defective FVIII binding, etcetera) and try to address these specific defects. Indeed, VWD is a heterogeneous disease, and the bleeding tendency is variable between the different VWD types. By focusing on the specific defect of the VWF protein, it would be possible to serve the specific needs of patients having similar functional or structural defects, rather than using a one-size-fits-all approach using full-length VWF.

In this review, we will focus on two potential options to expand the weaponry available to the clinician to manage VWD, with particular reference to a defect-specific approach: the bispecific antibody emicizumab and the aptamer BT200.

### **Correcting FVIII-deficiency in VWD**

VWF functions as a chaperone-protein for FVIII in the circulation by forming a tight non-covalent complex, and when VWF is unable to perform this chaperone-function, FVIII is eliminated rapidly from the circulation.<sup>25,26</sup> FVIII binding can be impaired in the presence of specific mutations within the FVIII-interactive site (referred to as VWD-type 2N), and patients with these mutations manifest a bleeding phenotype resembling those of hemophilia A patients.<sup>27</sup>

A secondary deficiency of FVIII is also observed in patients with VWD-type 3, who have a virtual absence of VWF antigen. The bleeding phenotype in VWD-type 3 patients is therefore more complex as a result of a combined deficiency of VWF and FVIII. It is difficult to estimate which portion of the bleeding phenotype is due to the absence of VWF and which portion is due to the absence of FVIII. Nevertheless, some insight into the contribution of FVIII-deficiency to the bleeding phenotype in VWD-type 3 patients has been obtained from treating these patients with recombinant VWF-free FVIII concentrates during surgical interventions. In four different cases (abdominal surgery<sup>28</sup>, cesarean section<sup>29</sup>, teeth extraction<sup>30</sup> and orthopedic surgery<sup>31</sup>), the use of recombinant FVIII resulted in sufficient hemostatic activity, suggesting that by increasing FVIII levels an important part of the bleeding phenotype can be corrected.

For long-term treatment of VWD-type 3 patients, the use of recombinant FVIII concentrates is not very practical, given its short half-life and the need for frequent intravenous infusions. However, the arrival of the bispecific antibody emicizumab opens another perspective in this regard. Emicizumab mimics some of the cofactor activities of FVIII, and its use in hemophilia A patients is associated with marked reductions in annualized bleeding rates.<sup>32</sup> Importantly, emicizumab has a half-life of about 4 weeks, allowing it to be applied subcutaneously in a weekly or biweekly fashion. As such, emicizumab could be an alternative to FVIII in the treatment of VWD-type 3 or type 2N to compensate for the absence of FVIII. An early example of how emicizumab could be beneficial to reduce the bleeding tendency in VWD-type 3 patients was reported by Weyand and colleagues in 2021.<sup>33</sup> They described the case of a young boy with VWD-type 3, who had developed antibodies against both VWF and FVIII upon treatment with VWF/FVIII concentrates (Fig. 1). Subsequent change to off-label treatment with

recombinant factor VIIa (270 $\mu$ g/kg; 3 times/week) did little to resolve the bleeding complications. The patient was then transitioned to daily infusions using activated prothrombin complex concentrates (100 U/kg) initially, which was reduced to three times/week later on. Unfortunately, this treatment still required co-treatment with recombinant factor VIIa upon breakthrough bleeds, and the treatment burden was experienced as being too heavy. At this point, the treating physicians decided to initiate off-label treatment with emicizumab (4 weeks of loading dose (3 mg/kg), followed by 1.5 mg/kg once weekly) given subcutaneously. Surprisingly, the patient remained free of spontaneous bleeding complications during the following 9 months of follow up, and required a single additional treatment with recombinant factor VIIa upon a trauma-induced soft tissue hematoma. Apparently, correcting FVIII deficiency using emicizumab proved to be of benefit in this particular case.

At this moment, several additional cases of off-label use of emicizumab in VWD patients have been reported, some in abstract form and some as case reports (for review see Thomas and colleagues).<sup>34</sup>

In general, emicizumab use has been associated with a markedly improved hemostatic profile, manifested by reduced or lack of hospitalisations, transfusions, joint bleeds and major spontaneous bleeds. It thus seems that correcting the FVIII deficiency in VWD-type 3 ameliorates the bleeding phenotype in these patients. Given the long half-life of emicizumab, its possibility to be applied subcutaneously and the promising data reported regarding VWD-type 3, it would be of interest to evaluate its efficacy in an appropriately designed clinical study. It should be noted that also efanesoctocog/BIVV001, a FVIII-variant having a half-life of 38-43 h<sup>35</sup>, could be of relevance in this regard.

Could emicizumab or efanesoctocog also be efficient in other types of VWD? Naturally, one would think of VWD-type 2N, where VWF functions normally in the process of platelet recruitment, but lacks its protective action towards FVIII. As for emicizumab, a recent study evaluated its effect on ex vivo thrombus formation in a microfluidic perfusion chamber using blood from 5 different VWD-type 2A patients.<sup>36</sup> VWF:RCo/VWF:Ag ratios were  $\leq 0.35$ , while FVIII activity levels were 20-40%. As expected, the addition of VWF (1.6 U/ml) to the patients' blood increased surface coverage and thrombus height



5-6-fold upon perfusion over a collagen-surface. In contrast, the addition of FVIII (1 U/ml) had little or any effect. It was surprising therefore that the addition of emicizumab (100 µg/ml) increased both surface coverage and thrombus height 3-4-fold. While it is yet unclear by which mechanism emicizumab improves thrombus formation under these conditions, these in vitro data are encouraging and favor further research in this direction.

### **Increasing endogenous VWF levels**

Desmopressin has been a powerful tool in the treatment of patients with VWD-type 1, as it induces a rise in VWF levels to achieve improved hemostatic activity.<sup>9,37</sup> However, post-treatment increases of VWF are transient and limited by the short half-life of VWF, and repetitive use results in diminished responsiveness (tachyphylaxis).<sup>37</sup> Also, desmopressin has variable efficacy in VWD-type 2A and 2M, is contra-indicated for VWD-type 2B, and cannot be used in the vast majority of VWD-type 3 patients.<sup>37</sup> An alternative approach to increase VWF levels in the patient could be by delaying its clearance rather than to enhance its production or secretion. Clearance of VWF can be delayed by bridging it for example to endogenous albumin or IgG, driving VWF into the FcRn-mediated recycling pathway, or by directly preventing its interaction with clearance receptors.

Several clearance receptors for VWF have been described, including LRP1, CD204/SR-AI, Stabilin-2, CLEC4M and Macrophage galactose-type lectin.<sup>38-42</sup> In vitro and in vivo studies have shown that blocking the binding of VWF to these receptors interferes with its cellular uptake and prolongs its circulatory half-life.<sup>38-42</sup> It would be of interest to develop agents that interfere with the binding of VWF to one or more of these receptors, while maintaining the functional integrity of VWF.

A first step in this direction has already been made by Kovacevic and colleagues, who recently described an aptamer (designated BT200) that seems to interfere with the clearance of VWF.<sup>43</sup> BT200 is a short hairpin-structured oligonucleotide, and is an optimized derivative of the previously described aptamer ARC1779.<sup>44</sup> Both aptamers bind to the VWF A1 domain and block its interaction with the platelet-receptor Glycoprotein Ib $\alpha$ .<sup>45</sup> Indeed, BT200 was originally developed as an inhibitor of VWF-

platelet interactions, aiming the treatment of thrombotic complications.<sup>44</sup> In preliminary studies using ARC1779, it was observed that the infusion of this agent in VWD-type 2B patients was not only associated with increased platelet counts by preventing the formation of VWF/platelet complexes, but also with increased VWF levels.<sup>46</sup> This latter aspect has now been evaluated in a more detailed manner using the improved derivative BT200 in a dose-escalation study in human volunteers.<sup>43</sup> A dose-dependent increase in VWF and FVIII levels were observed upon repetitive, subcutaneous treatment using BT200 (0.18-36 mg). Maximal increase was 3-4 fold for VWF and 2.5-fold for FVIII (Figure 2). Interestingly, the same aptamer has also been tested in hemophilia A patients, finding that BT200 increases endogenous FVIII levels about 2-fold, and prolongs the half-life of exogenously administered FVIII concentrates 2-7 fold.<sup>47</sup> These preliminary data are more than promising, but of course additional clinical evaluation is still necessary. For example, it is worth noting that low plasma levels of BT200 ( $\geq 0.7$   $\mu\text{g/ml}$ ) are associated with prolonged collagen/ADP closure times ( $\geq 140$  s) in the platelet function analyzer.<sup>43</sup> It is essential therefore to find the optimal dosing that allows increased FVIII and VWF levels without compromising the patient's hemostatic activity. Furthermore, it would be necessary to identify which types of VWD would benefit from this molecule. Akin to desmopressin, BT200 would probably not be very useful in VWD-type 3, as VWF levels are virtually absent. Also, it remains to be investigated how effective it will be to increase levels of functionally inactive VWF variants in VWD-type 2A, VWD-type 2M or VWD-type 2N.

In summary, there is accumulating evidence from preclinical and clinical studies that other strategies than desmopressin can result in prolonged increase of endogenous VWF and FVIII levels. It seems conceivable that such approaches may find their place in the arsenal of treatment options that the clinician has available in the management of VWD.

## **Conclusion**

The development of alternative treatment options for hemophilia A has left some VWD patients with the question whether such innovative paths are also on the horizon for them. Fortunately, we can now

answer this question positively. In this review, we described two options, which at the relative short term could become available for these patients. A more extensive description of the different opportunities for innovation was published in 2021.<sup>10</sup> These innovative paths are not only limited to protein-based strategies but also genetic approaches are in early stage preclinical development. With genetic approaches, one should think of siRNA-based techniques to silence mutant alleles or even gene therapy.<sup>48-50</sup> However, many hurdles are there to take in order to make these approaches clinically viable.

Apart from the technical aspects, also other issues are of relevance for innovative agents becoming available for patients. There should be the support from clinicians themselves to welcome such new products, and of industry to believe that such products are viable from a commercial point of view. Only together (researchers, clinicians and other health care professionals, industry and patient groups) it is possible to enter a brighter future in which the quality-of-life standards for VWD patients are finally being improved.

### **Author contributions**

All authors contributed to the writing of the manuscript.

### **Conflict of interest**

PJL declares to receive research funding from the Agence National de la Recherche, Pfizer, Roche, Sanofi and Sobi, and speakers fees from CSL Behring, LFB Biomédicaments, Sanofi, Sobi. CKM and CC declare no conflict of interest

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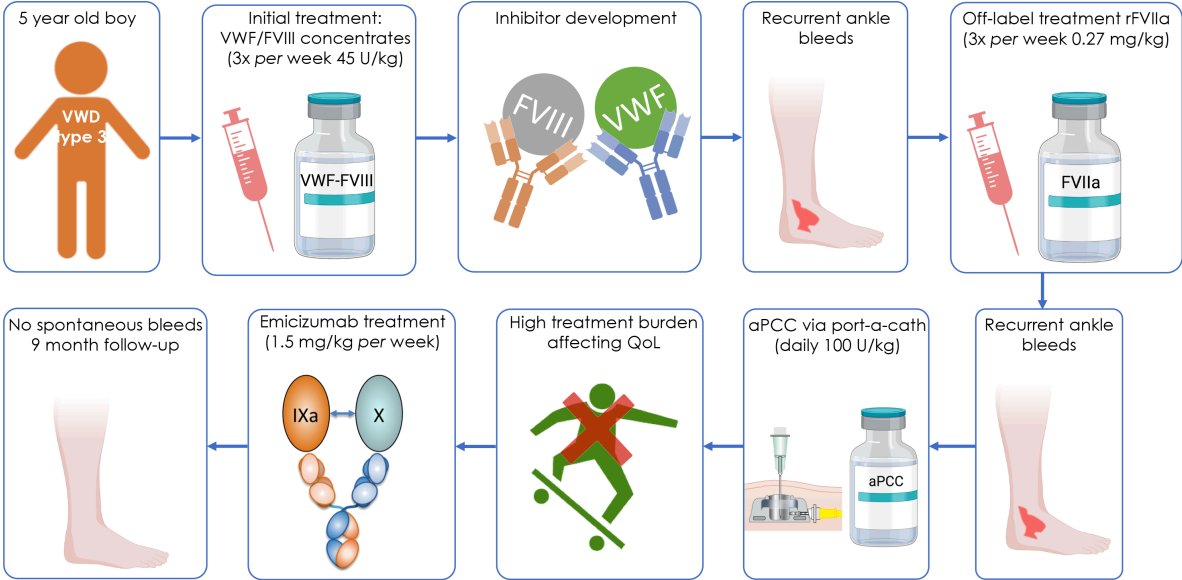
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**Figure 1: Emicizumab for VWD-type 3.** Early case report by Weyand and colleagues on the off-label use of emicizumab in a young boy with VWD-type 3 and inhibitors against both FVIII and VWF. Portions of this figure were created using Biorender.com



**Figure 2: Aptamer BT200 increases endogenous FVIII and VWF levels.** BT200 is a pegylated aptamer that binds to the VWF A1 domain. This aptamer has been shown to reduce clearance of the VWF/FVIII complex, resulting in a transient increase in plasma levels of both proteins. Its use in normal volunteers is associated with VWF levels being increased 3-4 fold, while its use in mild/moderate hemophilia A patients increase FVIII levels 2-3 fold.<sup>43,47</sup>

