Towards personalised therapy for von Willebrand disease: a future role for recombinant products

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Abstract
von Willebrand disease (VWD) is reportedly the most common bleeding disorder and is caused by deficiencies and/or defects in the adhesive plasma protein von Willebrand factor (VWF). Functionally, normal VWF prevents bleeding by promoting both primary and secondary haemostasis. In respect to primary haemostasis, VWF binds to both platelets and sub-endothelial matrix components, especially collagen, to anchor platelets to damaged vascular tissue and promote thrombus formation. VWF also stabilises and protects factor VIII in the circulation, delivering FVIII to the site of injury, which then facilitates secondary haemostasis and fibrin formation/thrombus stabilisation. As a result of this, patients with VWD suffer a bleeding diathesis reflective of a primary defect caused by defective/deficient VWF, which in some patients is compounded by a reduction in FVIII. Management of VWD, therefore, chiefly entails replacement of VWF, and sometimes also FVIII, to protect against bleeding. The current report principally focuses on the future potential for "personalised" management of VWD, given the emerging options in recombinant therapies. Recombinant VWF has been developed and is undergoing clinical trials, and this promising therapy may soon change the way in which VWD is managed. In particular, we can envisage a personalised treatment approach using recombinant VWF, with or without recombinant FVIII, depending on the type of VWD, the extent of deficiencies, and the period and duration of treatment.

Keywords: von Willebrand disease, treatment, management, recombinant VWF, recombinant FVIII.

Introduction
The current review provides a brief overview of the diagnosis of congenital von Willebrand disease (VWD), but primarily covers the management of this disorder from the perspective of biological replacement therapy. It provides a particular focus on emerging therapies related to recombinant products, namely recombinant von Willebrand factor (rVWF), and its potential use with recombinant factor VIII (rFVIII). A comparison of current factor concentrates and their limitations will also be made. These emerging potential approaches to therapy in VWD will have significant implications for future practice in transfusion medicine.

von Willebrand factor disorders
von Willebrand factor (VWF)-related disorders comprise both acquired von Willebrand syndrome (AVWS) and congenital von Willebrand disease (VWD), considered the most common inherited bleeding disorder. Both AVWS and VWD are due to deficiencies and/or defects in the plasma protein VWF\(^1-3\). The true prevalence of VWD is not known, but epidemiological studies estimate they involve up to 1% of the general population\(^4\); however, based on clinical presentations of symptomatic patients, a more conservative prevalence would be around 1 in 10,000 (0.01%). AVWS arises as an acquired disorder from a variety of causes\(^5,6\), but essentially still expresses clinical bleeding from "deficiency of VWF".

The complexity of plasma von Willebrand factor: production, secretion, and functional properties
A full discussion of this topic is beyond the scope of this review, but a synopsis will provide an important background to the diseases. VWF is a large and complex protein with essential roles in both primary and secondary haemostasis (see Sadler et al\(^1\), Yee and Kretz\(^6\), and Peyvandi et al\(^7\) for more extensive reviews). In vivo biosynthesis of VWF is limited to endothelial cells and megakaryocytes\(^8,9\). VWF is initially constructed as a pre-propolypeptide configuration, comprising a 22 amino acid signal peptide (pre), a 741 amino acids pro-polypeptide, and the remaining mature VWF subunit of 2,050 amino acids. After synthesis in the endoplasmic reticulum of endothelial cells, the signal peptide is cleaved, and oligosaccharide chains are added using N-linked glycosylation. Dimerisation of pro-VWF molecules then occurs through "tail-to-tail" inter-subunit carboxyl termini disulphide bond formation (Figure 1). The N-linked oligosaccharide chains are further modified in the Golgi apparatus by a series of glycosidases and glycosyltransferases to produce complex type...
carbohydrates, and additional oligosaccharide chains are added to each VWF monomer. Multimerisation of pro-VWF dimers then takes place in the post-Golgi, involving another round of disulphide bond formation near the amino-termini of the subunits. Additional modifications in the trans-Golgi network include the proteolytic removal of the large VWF propeptide, which is known to play an essential role in the multimer assembly (since deletion of the propeptide abolishes multimerisation), but which is not required for VWF function in plasma.

Mature VWF is then found in the plasma as a series of oligomers containing variable numbers of subunits (ranging from a minimum of 2 to a maximum 40) with the largest multimers having molecular weights in excess of 20,000 kDa. The VWF is either released directly into the plasma through a constitutive secretory pathway, or tubulised and stored in internal organelles known as Weibel-Palade bodies to be released later as required.

Upon exocytosis, rapid unfolding of VWF into ultra-long strings occurs, with VWF "docking" on the endothelial cells to permit adhesion to platelets. Thus, VWF stored within Weibel-Palade bodies of endothelial cells is composed of the largest multimeric species, ultra-large VWF (UL-VWF), which are usually not observed in normal plasma because of ADAMTS-13 (a disintegrin- and metalloprotease with thrombospondin type 1 motif, member 13) cleavage at the time of secretion. Regulated secretion of stored VWF from endothelial cells occurs in response to several physiological relevant agonists, including histamine and thrombin. VWF multimers and the VWF propeptide are actually secreted together in 1:1 stoichiometric amounts, but subsequently have different fates; the propeptide dissociates from VWF multimers and circulates independently as a non-covalent homodimer with a very short half-life of around 2 hours.

The D'-D3 domains of VWF represent the binding site for factor VIII (FVIII), and mutations in this region can lead to type 2N VWD (Figure 1). The D'-D3 domains are also possible binding sites for P-selectin, which has been found to anchor newly released ultra-large VWF to the surface of activated endothelial cells and thus present the VWF cleavage site to ADAMTS-13. The A1 domain represents the binding site for the platelet glycoprotein 1b (GPIb), as well as binding sites for heparin, sulphated glycolipids, the snake venom botrocetin, and some forms of collagen, notably type VI. The A2 domain contains the ADAMTS-13 cleavage site. The A3 domain is the binding site for fibrillar collagen (types I and III), and the C1 domain comprises the RGD sequence, being the binding site for the platelet integrin αIIbβ3 (GpIIb/IIIa) (Figure 1).

Figure 1 - The domain structure of von Willebrand factor showing ligand binding sites and formation of multimers.

von Willebrand factor function

Briefly, VWF is an adhesive protein that permits platelets to adhere to each other and to subendothelial matrix components such as collagen after tissue injury (primary haemostasis)\(^1,6,7\). Moreover, VWF binds to factor VIII (FVIII), thereby protecting this latter protein from proteolysis in the circulation and preserving its important (secondary) haemostatic functions. VWF, therefore, essentially delivers and localises platelets (containing an armamentarium of pro-coagulant material) as well as FVIII to the site of tissue injury, contributing to processes of both primary and secondary haemostasis (i.e. coagulation), promoting thrombus formation, and facilitating sealing and repair of the injured site. VWF achieves these functions thanks to the presence of various ligand-binding sites on the protein, as well as the multimeric structure of the mature protein.

The classical treatment for von Willebrand factor disorders: "one size fits all"?

Considering its functional properties, deficiencies and/or defects in VWF are, therefore, associated with a substantial risk of bleeding. The main aim of treatment is to replace the missing or defective VWF, but sometimes also FVIII may be lacking. Accordingly, therapeutic management is primarily achieved using VWF concentrate therapy, typically also containing FVIII, although in some cases desmopressin (1-deamino-8-arginine vasopressin [DDAVP]) therapy, which facilitates release of endogenously stored VWF, may also be used.

To some extent, the presenting haemorrhagic diathesis can be related to the degree of VWF:FVIII deficiency, the type of VWF defect, and/or the severity of the VWF defect. For example, in the most severe case of deficiency (i.e. type 3 VWD), there is a complete absence of VWF\(^1,2\). In terms of primary haemostasis, bleeding in VWD is typically mucocutaneous (i.e. menorrhagia, epistaxis, gum bleeds, gastrointestinal bleeds, etc.). However, because VWF is missing, the normally produced plasma FVIII is largely absent and what little there is cannot be protected against proteolysis. Thus, the deficiency of FVIII will also contribute to bleeding events in a secondary picture that is more typical of haemophilia A (i.e. muscular haematomas, joint bleeds, post-surgical bleeding from large wounds, etc.). Therapy for type 3 VWD would aim, therefore, to replace both the missing VWF and FVIII.

To a lesser extent, type 1 VWD, which is characterised by a quantitative loss of VWF, will also lead to some relative reduction also of FVIII, although some patients will have normal levels of FVIII. In other cases of VWD, abnormalities in VWF may be localised within discrete sections of the molecule and cause more specific problems\(^1,2,10\). These reflect a qualitative VWF disorder, representing a type 2 VWD. A specific defect may, for example, affect the ability of VWF to bind to platelets, whereas other abnormalities may impair the ability of VWF to bind to subendothelial matrix components such as collagen. These cases are mostly represented by types 2A and 2M VWD. In both these cases, there is a failure or reduction in the ability of platelets to effectively bind to injured tissue, and thus thrombus formation is compromised to varying extents (depending on the type of defect), albeit through different mechanisms. In many of these patients, FVIII levels are normal, and therapy should, therefore, generally be aimed at correcting only the missing functional VWF.

Another form of VWD is type 2N VWD\(^1\), which describes a specific VWF defect where binding to FVIII is impaired. In these patients, like in type 3 VWD, plasma FVIII remains unprotected and vulnerable to early proteolysis, so that the bleeding symptoms actually mimic those of haemophilia A. However, VWF levels and other VWF functions are often preserved in type 2N VWD, hence mucocutaneous bleeding is less common, and the therapy should mainly address the missing FVIII.

To summarise, VWF represents a large, complex and multi-function plasma protein that contributes to haemostasis in a multitude of ways. VWD arising from deficiencies or defects in VWF may show somewhat variable clinical presentations depending on the type and extent of the defect/deficiency. Thus, some patients with VWD suffer from a combination of bleeding issues related to loss of VWF as well as FVIII, whereas others will primarily suffer mucocutaneous bleeding symptoms. Although the aim of biological replacement therapy is to correct the underlying defect by providing VWF (and only sometimes FVIII)\(^1\), ideally, differential therapy would be given to different people with VWD on the basis of the type and extent of the VWF abnormality/deficiency, as well as the duration of treatment. However, the biological therapies that are currently available typically represent VWF concentrates with added FVIII concentrate according to local availability; a "one size fits all" approach that is not ideal.

von Willebrand factor excess is associated with thrombosis

The other side of the haemostasis coin that is VWD (deficiency of VWF) is the risk of thrombosis from excess VWF (and/or FVIII), an issue which is extremely important to any discussion of therapy both in VWD and in rVWD. In normal individuals, the levels of plasma VWF and FVIII are regulated to within a tight physiological range. When levels fall below this range, there is a risk of bleeding (e.g. VWD or haemophilia A), and when levels are above this range...
Recombinant VWF therapy for VWD

there is a risk of thrombosis. The risk of thrombosis can occur when FVIII or VWF levels are high, or when there is an excess of high molecular weight (HMW) VWF forms; the latter is represented by congenital (Upshaw–Schulman syndrome) or acquired forms of thrombotic thrombocytopenic purpura (TTP), caused by a deficiency of or antibodies to ADAMTS-13. As noted previously, ADAMTS-13 cleaves HMW VWF during secretion or at sites of vascular attachment, and this normally prevents downstream accumulation of the very adhesive UL-VWF multimers. Deficiency in ADAMTS-13 activity can, therefore, lead to conditions predisposing to thrombosis12-16. In addition, thrombosis may occur due to overaccumulation of VWF or FVIII, and this may occur in normal individuals or in VWD/VWS treatment as a consequence of VWF/FVIII replacement therapy17,18. The relevance to rVWF is that in vitro produced rVWF has never been exposed to ADAMTS-13, and so its composition varies from that of native plasma VWF, including higher expression of HMW VWF forms such as UL-VWF. Depending on the in vitro cell system used, rVWF may also be secreted without deletion of the pro-VWF fragment, without appropriate carbohydrate processing/glycosylation, or with different glycosylation (see the section on rVWF).

Diagnosis of VWD points to potential differential therapy

A fully comprehensive review of the diagnostic and laboratory testing for VWD and AVWS is beyond the scope of the current review, and has been addressed in detail elsewhere13,11,19-29. Nevertheless, an overview is important as this can then help to determine the most appropriate therapy. Congenital VWD arises from deficiency and/or defects in VWF, most commonly due to mutation/s in the VWF gene, mapped at 12p13.3. VWD diagnosis requires the presence of a personal, typically lifelong, family history of primarily mucocutaneous bleeding, as well as laboratory evidence of absence, deficiency or defect in VWF13,26-29. Young patients may present no historical evidence of "lifelong" bleeding or this may be limited. Diagnosis of AVWS requires similar evidence of bleeding and lack, deficiency or defect in VWF; but often there is no family history of the disease and personal history is not usually lifelong34.5.

Appropriate laboratory testing is critical in the diagnostic strategy and should include assays for VWF level and activity, as well as FVIII activity13,26-29. The more comprehensive the test panel, the more likelihood there is of obtaining a correct diagnosis; the smaller and more incomplete the test panel, the greater the risk of mis- or non-diagnosis30. VWF testing must include determining a "level" of plasma VWF, which is typically assessed using an antigen assay (VWF:Ag). In addition, because of the many activities represented by functional VWF, and the heterogeneity of VWD/VWS, assessment of VWF activity requires many tests26-32. Such tests should include assessment of VWF platelet adhesion, which is most commonly assessed using a ristocetin co-factor (VWF:RCo) assay (although there are several alternative assays available or under development) as well as VWF binding activity associated with subendothelial collagen adhesion, which is generally assessed using a collagen binding (VWF:CB) assay. Evaluation of VWF-FVIII binding function, critical for proper identification of type 2N VWD, is also useful and is assessed using a VWF:FVIII binding (VWF:FVIIIIB) test. Another functional assay that is more selectively used in VWD diagnosis (but which is critical for identification and differentiation of types 2B and PT-VWD) is the ristocetin induced platelet aggregation (RIPA) assay. VWF multimer assessment to check for any loss of HMW VWF or for any abnormal VWF bands may also be useful, although some laboratories use the various activity assays, especially VWF:RCo and VWF:CB, as surrogates for multimer assessment32.

According to the current classification scheme1, there are 6 types of VWD (Table I). These are characterised on the basis of quantitative deficiencies of VWF (VWD types 1 and 3) or qualitative defects in VWF (type 2 VWD), which may or may not be also associated with a quantitative deficiency of VWF. Some forms of AVWS essentially mimic type 1 VWD and are also due to quantitative deficiencies in VWF: i) hypothyroidism, where reduced VWF production is hypothesised; ii) mechanisms that increase VWF clearance from the plasma, e.g. via immune autoantibodies or absorption onto cellular surfaces, such as transformed or cancer cells or platelets. In other cases, AVWS may reflect a qualitative defect; for example, aortic stenosis and plasma cell disorders may induce a selective removal of HMW VWF.

Type 1 VWD defines a quantitative deficiency of VWF (the plasma VWF is otherwise functionally normal) and is the most common form of VWD in developed countries (40-70% of all cases3). The severity of the bleeding diathesis is directly related to the extent of the deficiency. FVIII falls in parallel with VWF, but is normally present at higher levels than VWF. Type 1 VWD (or AVWS) is identified by a similar concordant loss of both VWF:Ag and VWF activity, and all VWF assays will show similar decreases, with all VWF assay ratios being above 0.7. VWF multimers will show the presence of reduced intensity consistent with loss of VWF, but the presence of all VWF multimer forms. Optimising therapy would involve replacing the missing VWF, aiming to increase levels to normal, and, only if required, also FVIII levels (Table I).
Type 3 VWD defines the most severe defect in this patient cohort, essentially describing an absence of VWF and representing a rare form of VWD in developed countries (<5% of all VWD cases). Type 3 VWD will typically show an absence of VWF by all assays, although in many laboratories this will be compromised by issues concerning the lower limit of VWF detection. In practice, identifying levels of less than 5 U/dL for each VWF assay is usually sufficient for a diagnosis. FVIII level and activity is also typically low (e.g. <10 U/dL), and VWF multimers will only confirm an absence of VWF. Therapy is based on replacing the missing VWF, aiming to increase levels to normal, but here there is a need to replace both VWF and (at least initially) also FVIII, although the latter can be tapered off or omitted once the exogenously provided VWF binds to and protects the patient’s endogenously produced FVIII (Table I). This typically occurs within approximately 24 hours of treatment.

In Type 2 VWD patients, characterised by qualitative defects of VWF, the level of VWF protein may be normal or reduced, and FVIII levels may also be low or normal. Type 2 VWD will essentially provide different test patterns to type 1 and 3 VWD,

Table I - Classification scheme for von Willebrand disease, phenotypic presentation, and therapy considerations.

<table>
<thead>
<tr>
<th>VWD type</th>
<th>Description</th>
<th>Incidence</th>
<th>Phenotypic diagnosis</th>
<th>Therapy considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Partial quantitative deficiency of VWF.</td>
<td>Most common presentation of “VWD” to most laboratories, with most patients presenting with mildly reduced levels of VWF.</td>
<td>Low levels of VWF, with VWF functional concordance (i.e. ratio of functional VWF/VWF:Ag approximates unity).</td>
<td>Usually respond well to desmopressin, unless FVIII &lt;10U/dL. VWF concentrate required for desmopressin non-responders or for long-term therapy. Need to replace VWF and sometimes also FVIII.</td>
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<tr>
<td>2A Decreased VWF-dependent platelet adhesion and a selective deficiency of high molecular weight (HMW) VWF multimers.</td>
<td>Globally considered to be the most common presentation of type 2 VWD.</td>
<td>Loss of HMW VWF. Usually low levels of VWF, with VWF functional discordance (i.e. ratios of RCo/Ag and CB/Ag typically &lt;0.7).</td>
<td>Variable clinical response to desmopressin. VWF concentrate represents most common therapy. Need to replace (HMW) VWF and sometimes also FVIII.</td>
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</tr>
<tr>
<td>2B Increased affinity of VWF for platelet glycoprotein Ib.</td>
<td>Rare form (generally 10-20%) of Type 2 VWD (~1-5 cases per million population). Defined by enhanced responsiveness in a RIPA assay.</td>
<td>Low to normal levels of VWF, typically with VWF functional discordance (i.e. ratios of RCo/Ag and CB/Ag generally &lt;0.7), loss of HMW VWF and (mild) thrombocytopenia. Atypical cases may not show this pattern.</td>
<td>Desmopressin use is contentious (believed contraindicated by some; whereas others feel this may represent an effective treatment in a proportion of patients). VWF concentrate represents most common therapy. Need to replace (HMW) VWF and only rarely also FVIII.</td>
<td></td>
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<tr>
<td>2M Decreased VWF-dependent platelet adhesion without a selective deficiency of high molecular weight (HMW) VWF multimers.</td>
<td>Under-recognised form of Type 2 VWD. Probably as common as 2A VWD.</td>
<td>Low to normal levels of VWF, usually with VWF functional discordance detected by RCo/Ag generally &lt;0.7, but relatively normal CB/Ag ratio. HMW VWF present, but multimers may show other abnormalities.</td>
<td>Variable clinical response to desmopressin and VWF concentrate represents most common therapy. Need to replace functional VWF and sometimes also FVIII.</td>
<td></td>
</tr>
<tr>
<td>2N Markedly decreased binding affinity for factor VIII.</td>
<td>Rare form (generally &lt;10%) of Type 2 VWD (~1-5 cases per million population).</td>
<td>Defined by VWF:FVIIIIB assay, with low FVIIIIB/VWF ratios.</td>
<td>Variable clinical response to desmopressin and VWF concentrate represents most common therapy. Need to replace functional VWF and also sometimes FVIII.</td>
<td></td>
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<tr>
<td>3 Virtually complete deficiency of VWF.</td>
<td>Rare form of VWD in developed countries (~1-5 cases per million population), but disproportionately more common in developing countries.</td>
<td>Typically defined by VWF levels &lt;2U/dL and FVIII &lt;10U/dL.</td>
<td>Desmopressin ineffective, and VWF concentrate represents only effective therapy. Need to replace VWF and also FVIII, at least initially. Once stable infused VWF levels (“steady state”) reached, FVIII levels will rise due to stabilisation of endogenous FVIII, and FVIII transfusion will no longer be required.</td>
<td></td>
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</table>

Classification scheme derived and adapted from Sadler et al.1 Table modified from Favaloro et al.10 CB/Ag: collagen binding to antigen ratio; DDAVP: desmopressin; HMW: high molecular weight; FVIII:C: factor VIII coagulant; LOD: limit of detection; RCo/Ag: ristocetin cofactor to antigen ratio; RIPA: ristocetin-induced platelet agglutination (aggregation); VWD: von Willebrand disease; VWF: von Willebrand factor; VWF:CB: von Willebrand factor collagen binding; VWF:Ag: von Willebrand factor antigen; VWF:FVIIIIB: VWF FVIII binding assay; VWF:RCo: von Willebrand factor ristocetin cofactor.
with these providing the diagnostic clues for the VWD type present\textsuperscript{1,3,26-32}. Type 2A VWD describes an absence or deficiency in high molecular weight (HMW) VWF\textsuperscript{1}, the form of VWF that is most biologically active. Type 2A VWD is classically considered the most common form of type 2 VWD, although type 2M VWD may be as common\textsuperscript{1}. Type 2A VWD (or Type 2 AVWS) will typically show a loss of VWF:Ag, but both VWF:CB and VWF:RCo will be lower, and collagen binding to antigen (CB/Ag) and ristocetin co-factor to antigen (RCo/Ag) ratios typically below 0.6. VWF multimers will show a loss of HMW VWF. Replacement therapy aims to provide functionally normal VWF; however, these patients have variable levels of low molecular weight VWF, so a more ideal state for replacement therapy might be selective replacement of HMW VWF. FVIII may or may not also need to be replaced (Table I).

Type 2B VWD describes patients in whom VWF is hyper-adhesive\textsuperscript{1}, which is then cleared from the circulation with "spontaneously" bound platelets, leading to a loss of HMV VWF, and also sometimes mild thrombocytopenia. Type 2B VWD is a relatively rare form of type 2 VWD, affecting less than 5% of all VWD patients\textsuperscript{1}. Type 2B cases will usually show a similar plasma phenotypic pattern to type 2A, except that the relative loss of VWF:CB and VWF:RCo is less severe. These patients will also show enhanced binding in a RIPA assay, and VWF multimers will typically show a loss of HMW VWF. Replacement therapy aims to provide functionally normal VWF, but as these patients have normal levels of low molecular weight VWF, a more ideal state for replacement therapy might be selective replacement of HMW VWF. FVIII may or may not also need to be replaced (Table I).

Type 2N VWD reflects a defect in VWF that does not permit proper binding to FVIII\textsuperscript{1} and is a relatively rare form of type 2 VWD, affecting less than 5% of all VWD cases\textsuperscript{1}. Like type 3 VWD, this leads to early proteolysis and loss of plasma FVIII, with consequent bleeding symptoms similar to those of haemophilia A. Replacement therapy aims to replace VWF (rather than FVIII), because therapy with FVIII only provides short-term benefit (the replacement FVIII is rapidly degraded), whereas replaced VWF binds to and protects the patient's endogenously produced (normal) FVIII. Since the VWF in these patients is otherwise functionally normal, replacement therapy could be better targeted to provide VWF capable of binding and stabilising FVIII function; here, low molecular weight forms of VWF could theoretically be used for this purpose. FVIII therapy may be needed in some patients as initial therapy where low levels of FVIII are expressed; this could be tapered off or omitted in subsequent infusions as exogenously provided VWF stabilises endogenous FVIII (Table I).

Type 2M VWD describes qualitative defects not associated with loss of HMW VWF\textsuperscript{1}. Although classically considered a rare form of VWD, many cases of type 2M have been inappropriately misidentified as type 1 or 2A VWD\textsuperscript{1}, and so type 2M VWD is often misdiagnosed, and may be as common as type 2A VWD. Test patterns for type 2M VWD depend on the VWF defect, because this represents a heterogenous group. However, most 2M VWD cases so far described reflect platelet binding defects, so there will usually be a relative loss of VWF:RCo or GPIb binding activity, with VWF:CB activity less affected. VWF multimers will not show a loss of HMW VWF, but may display some abnormal banding patterns. Replacement therapy in 2M VWD aims to replace the dysfunctional VWF with functional VWF. FVIII may be low or normal and thus may or may not also need to be replaced (Table I).

For completeness, although platelet type (PT)-VWD is not considered a true VWD, since the defect lies in the platelet glycoprotein (GP) VWF receptor (GPIb), the laboratory phenotype of PT-VWD essentially mimics 2B VWD, including enhanced binding in a RIPA assay. However, in PT-VWD, the enhanced binding is due to the hyper-adhesive GPIb receptor, whereas for 2B VWD it is due to hyper-adhesive VWF. PT-VWD and 2B VWD are differentiated by RIPA mixing studies or by genetic analysis. PT-VWD is a rare disorder that occurs at the rate of approximately 10% that of type 2B VWD\textsuperscript{1}. Importantly, PT-VWD requires a different therapeutic management, based on platelet replacement rather than replacing VWF, which is already normal in these patients\textsuperscript{23-25}.

**Current therapies for von Willebrand disease: desmopressin and biological VWF concentrate Desmopressin**

Desmopressin reflects a non-transfusional form of VWD therapy, and essentially permits release of endothelial stored VWF into the circulation. Thus, desmopressin is only effective in those VWD individuals who produce some cellular VWF, and primarily those with type 1 VWD (unless base-line VWF levels are very low) (Table I). However, desmopressin may also be effective in selected patients with type 2 VWD, including 2A, 2M and 2N VWD (Table I)\textsuperscript{3}. Most experts do not recommend using desmopressin in type 2B VWD due to concerns over the potential resultant thrombocytopenia as the hyper-adhesive VWF spontaneously binds to and results in platelet clearance.
Desmopressin is most commonly administered intravenously, although subcutaneous preparations are available outside the USA3. Intranasal preparations are also produced; however, these vary in concentration and not all are widely available. A candidate for desmopressin should be tested for response ("desmopressin trial") prior to use as standard therapy; a test infusion of 0.3 μg/kg in 50 mL normal saline is typically administered intravenously over 30 minutes and the response assessed using pre- and post- (e.g. 1, 2, 4, 24 hour) infusion testing with factor VIII coagulant (FVIII:C), VWF:Ag and VWF:RCo (in our lab also VWF:CB and, if indicated, PFA-100 closure time)33,34. "Responders" (those identified as having an adequate response to desmopressin) show a 2- to 5-fold increase from baseline and have VWF and FVIII:C levels above 50 U/dL at 1 hour. Levels remain above 30 U/dL four hours post infusion unless VWF and/or FVIII clearance is significantly increased, but levels generally return to baseline by 24 hours3. Doses may be repeated for up to 72 hours but responses diminish due to depletion of VWF stores (termed tachyphylaxis).

As cellular VWF is usually normal in type 1 VWD, the majority of these patients demonstrate an increase in VWF levels of sufficient magnitude and duration to recommend it as first-line therapy for minor surgery and bleeding5. Furthermore, the response pattern is consistent within families, so that a parent's response may be useful to help predict that of an affected child. In type 2 VWD, responses to DDAVP are more variable, but some patients with 2A, 2N and 2M may benefit from its use3. Desmopressin is ineffective in type 3 VWD, as these individuals do not produce any VWF. Use of desmopressin in women requires special consideration, for example, to treat menorrhagia, or in the delivery room after section of the umbilical cord. However, its use during pregnancy is often avoided due to limited safety data2.

There are some potential adverse effects of desmopressin, including facial flushing, hypertension or hypotension, tachycardia, headache, gastrointestinal upset and hyponatremia, in some rare cases complicated by seizures. Myocardial infarction has rarely been reported and thus DDAVP should be avoided in patients with increased risk for cardiovascular and cerebrovascular disease2. Fluid restriction and monitoring of electrolytes is recommended when repeat doses are used.

**Biological VWF concentrates**

In general, factor replacement therapy is the mainstay of biological therapy for all factor deficiencies, including VWD, where desmopressin is not effective or sufficiently effective. However, a wide range of VWF concentrates are currently available worldwide, as summarised in Table II35-44. There are also several expert and national guidelines or recommendations for VWD treatment11.

Additional differential global features are worthy of note.

1) Most concentrates contain both VWF and FVIII, although they differ in terms of relative proportions (Table II); this has important implications in the context of therapeutic management.

2) Concentrates have different proportional levels of FVIII; some concentrates have relatively high, and others relatively low, and few concentrates are essentially FVIII deficient, or only contain VWF.

3) Production techniques for VWF concentrates vary, and consequently the retention or loss of HMW VWF also varies. As HMW VWF forms define the most adhesive or functional forms of VWF; an HMW-containing VWF concentrate would provide greater

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**Table II** - Summary of the major current VWF/FVIII concentrates: similarities and differences.

<table>
<thead>
<tr>
<th>Concentrate</th>
<th>Biostate®a</th>
<th>Haemate P®/Humate-P®b</th>
<th>Alphanate®c</th>
<th>Fanhdi®d</th>
<th>Immunate®e</th>
<th>Wilate®f</th>
<th>Wilfactin®g</th>
<th>Factor 8Y®h</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMW VWF ( % of NHP)</td>
<td>86</td>
<td>93.6</td>
<td>29.3</td>
<td>31.7</td>
<td>3.9</td>
<td>N/A</td>
<td>N/A</td>
<td>32.1</td>
<td>4-94</td>
</tr>
<tr>
<td>VWF:RCo/VWF:Ag</td>
<td>0.73-0.99</td>
<td>0.91</td>
<td>0.43</td>
<td>0.69</td>
<td>0.38</td>
<td>0.9-1.0</td>
<td>0.95</td>
<td>0.6</td>
<td>0.4-1.0</td>
</tr>
<tr>
<td>VWF:CB/VWF:Ag</td>
<td>0.72-0.95</td>
<td>0.89</td>
<td>0.49</td>
<td>0.47</td>
<td>0.21</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>VWF:RCo/FVIII:C</td>
<td>2.00</td>
<td>2.88</td>
<td>0.82</td>
<td>1.29</td>
<td>0.67</td>
<td>1.0</td>
<td>&gt;10</td>
<td>1.8</td>
<td>0.7-&gt;10</td>
</tr>
<tr>
<td>VWF:CB/FVIII:C</td>
<td>2.53</td>
<td>2.28</td>
<td>0.68</td>
<td>0.80</td>
<td>0.16</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.2-2.5</td>
</tr>
</tbody>
</table>

*aCSL Behring, Melbourne, Australia; bCSL Behring, King of Prussia, PA, USA; cGrifols, Los Angeles, CA, USA; dGrifols, Cambridgeshire, UK; eBaxter AG, Vienna, Austria; fOctapharma, Hoboken, NJ, USA; gLFB, Les Ulis, France; hBiotest Products Laboratory, Hertfordshire, UK. FVIII:C: factor VIII coagulant activity; HMW: high molecular weight; N/A: not available; NHP: normal human plasma; VWF: von Willebrand factor; VWF:Ag: antigen; VWF:CB: collagen binding assay; VWF:RCo: ristocetin cofactor. Data collated from various references35-44."
Recombinant VWF therapy for VWD

adhesive haemostatic efficacy than one relatively devoid of HMW VWF. Surrogate markers (e.g. RCo/Ag or CB/Ag ratios) can provide information on the level of "specific" VWF activity.\textsuperscript{26,27,32,45} (Table II).

4) Concentrates undergo treatment for removal and destruction of potentially infectious agents such as HIV or hepatitis viruses, and the type and extent of these treatments also differ among concentrates.\textsuperscript{39}

5) Although VWF concentrates are used for VWF replacement and treatment of VWD/AVWS, some are only labelled with FVIII levels, and/or dosed according to the level of FVIII and/or monitored by FVIII:C testing, perhaps reflecting regulatory restrictions preventing labelling of products with newer VWF activity levels.\textsuperscript{11,45} Nevertheless, as different concentrates vary widely in terms of relative VWF and FVIII level, dosing VWD patients by concentrate FVIII level is not ideal, and potentially hazardous if inappropriately applied\textsuperscript{11} (Table II).

Concentrates are normally managed by transfusion laboratories, and, once issued, are given intravenously to treat or prevent bleeds; efficacy is monitored clinically by laboratory tests using the same tests as used for VWD diagnosis.

Recombinant von Willebrand factor

The gene for VWF was cloned three decades ago by four independent groups\textsuperscript{46-49}, and rVWF conceived as a potential therapy in VWD soon thereafter.\textsuperscript{50-56} However, VWF is a complex molecule, including carbohydrate structure/glycosylation, assembly of multimers, and other processing steps to remove some elements (such as the pro-VWF polypeptide) or to otherwise modify its structure (such as ADAMTS-13). This makes its optimal production in \textit{in vitro} systems more difficult to achieve. Considering this, the initial construction of a recombinant form of VWF\textsuperscript{50-56} for potential therapy in VWD did not progress to human trials. Subsequently, a new cell line and production process was devised to generate a rVWF that was developed alongside rFVIII\textsuperscript{57,58}. To enable cleavage of the pro-VWF polypeptide, the processed rVWF includes a step that exposes it to the enzyme Furin. However, even the final formulation of this processed material has never been exposed to ADAMTS-13, and therefore still contains UL-VWF molecules. In addition, the typical multimer triplet pattern present in plasma derived VWF is not present in rVWF, since this is also caused by ADAMTS-13 exposure in plasma.

Other similarities and differences between plasma derived and recombinant VWF are highlighted in Table III. Given the differences identified, it was important to ascertain not only that rVWF yields equivalent or better functionality, but also that this material is safe. This particularly important in terms of potential thrombogenicity, given that excess VWF and excess UL-VWF are both risk factors for thrombosis. A large series of \textit{in vitro} and animal studies was undertaken to explore both efficacy and safety\textsuperscript{57-59}, including a re-evaluation of animal models to ensure suitability by effective species-related ADAMTS-13 cleavage of human rVWF.

Another important issue is the functionality of human rVWF; this was extensively and elegantly explored using a wide range of methodologies\textsuperscript{57-59}. These studies essentially showed similar or superior specific activity for rVWF compared to either plasma-derived VWF or comparator plasma-derived VWF concentrate. The most important findings from these studies are presented in Table III.

More recently, the first \textit{in human} (i.e. Phase I) trial to explore the safety and pharmacokinetics of rVWF was undertaken and published\textsuperscript{50}. This study built on the \textit{in vitro} and animal studies to show that the product was indeed safe (there were no serious adverse events, including thromboses), and that the specific VWF activity was also better or equivalent to the comparator (Humate\textsuperscript{®}/Haemate\textsuperscript{®}, CSL Behring, King of Prussia, PA, USA) VWF concentrate, chosen specifically because it was the only product licensed for VWD in all countries participating in the clinical trial. The main findings of this clinical trial are summarised in Table IV.

Very recently, a report of Phase III trial has also been published\textsuperscript{51}. This study built on the Phase I study to show that rVWF could be used with or without rFVIII for treatment of type 3 VWD, depending to some extent on the time of treatment. The main findings of this clinical trial were that use of rVWF with (or without) rFVIII is safe and haemostatically effective in severe VWD patients for a variety of bleeding symptoms. Moreover, use of rVWF induced sustained stabilisation of endogenous FVIII, which could obviate the need for rFVIII after the first infusion. The main findings of this clinical trial are summarised in Table V.

Towards personalised therapy in von Willebrand disorders

"One size" does not fit all and currently available VWF/FVIII concentrates are not identical

To summarise, currently available VWF concentrates differ widely on the basis of HMW VWF, specific VWF activities such as RCo/Ag, CB/Ag, RCo/FVIII, as well as other parameters, including pharmacokinetic profiles\textsuperscript{26-27} (Table II). Thus, some are theoretically more efficacious than others.

von Willebrand disease, although currently treated according to "standardised protocols", most often including factor concentrates that entail a combination of VWF plus FVIII locally using available concentrates,
### Table III - Comparison of plasma/plasma derived VWF, plasma derived VWF concentrates, and recombinant VWF.

<table>
<thead>
<tr>
<th>Product</th>
<th>Plasma/plasma-derived VWF</th>
<th>Plasma-derived VWF concentrates</th>
<th>Recombinant VWF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMW VWF (% of NHP)</td>
<td>100&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Variable&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;100</td>
<td>Recombinant VWF contains UL-HMW VWF (has never been exposed to ADAMTS-13)</td>
</tr>
<tr>
<td>Multimer Triple pattern</td>
<td>Normal</td>
<td>Normal</td>
<td>No triplet pattern</td>
<td>The triplet pattern of plasma VWF arises from ADAMTS-13 processing, which recombinant VWF has never been exposed to. Once introduced into normal plasma containing ADAMTS-13, recombinant VWF quickly forms the triplet pattern</td>
</tr>
<tr>
<td>Pro-VWF polypeptide</td>
<td>Cleaved from VWF prior to release into plasma</td>
<td>Unknown</td>
<td>Cleaved from recombinant VWF using Furin</td>
<td>Pro-VWF polypeptide is not required for mature VWF activity, and indeed may inhibit FVIII binding. The main role of the pro-VWF polypeptide appears to be to facilitate the multimatisation of VWF.</td>
</tr>
<tr>
<td>Carbohydrate structure/Glycosylation of VWF</td>
<td>&quot;Normal&quot; but some differences from individual to individual based on ABO blood group. Differences also in plasma VWF vs platelet-derived VWF.</td>
<td>&quot;Normal&quot; but some differences expected dependent on ABO blood group contributions from donor plasmas?</td>
<td>&quot;Similar&quot; to plasma VWF but exact nature is unclear. No ABO determinants, and possibly more like platelet VWF than plasma VWF.</td>
<td>Carbohydrate structure/glycosylation of VWF plays a role in VWF clearance from plasma, susceptibility to ADAMTS-13 cleavage and platelet GP Ib binding. Recombinant VWF has been reported to have a slower clearance than the comparator (Humate®/Humate®) in the human clinical trial. The potential influence of carbohydrate structure/glycosylation in this was not mentioned in the clinical trial publication, but might be implicated based on other literature.</td>
</tr>
</tbody>
</table>

**Specific VWF activities:**

| VWF:RCo/VWF:Ag | Variable, but typically ~<1<sup>a</sup> | >1 | |
| VWF:CB/VWF:Ag | Variable, but typically ~<1<sup>a</sup> | >1 | |
| VWF:RCo/FVIII:C | ~0.5-1 (plasma) | Variable<sup>b</sup> | >10<sup>c</sup> |
| VWF:CB/FVIII:C | ~0.5-1 (plasma) | Variable<sup>b</sup> | >10<sup>c</sup> |

<sup>a</sup>Theoretical/relative/reference values; <sup>b</sup>see Table II; <sup>c</sup>recombinant VWF only contains trace amounts of FVIII, but can be combined with recombinant FVIII in variable quantities.


### Table IV - Main findings from Phase I human recombinant VWF clinical trial.

<table>
<thead>
<tr>
<th>Product (parameter)</th>
<th>Recombinant VWF/ recombinant FVIII</th>
<th>Plasma-derived VWF/FVIII concentrate (Humate®/Haemate®)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (U/kg)</td>
<td>VWF:Ag</td>
<td>VWF:RCo</td>
<td>FVIII</td>
</tr>
<tr>
<td>AUC (0-4)</td>
<td>47.2 (7.5)</td>
<td>60.2 (9.6)</td>
<td>38.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cl</td>
<td>4.1 (3.1)</td>
<td>2.2 (2.5)</td>
<td>2.6 (7.5)</td>
</tr>
<tr>
<td>T1/2</td>
<td>16.3 (7.1)</td>
<td>25.5 (6.7)</td>
<td>-</td>
</tr>
<tr>
<td>MRT</td>
<td>23.6 (9.7)</td>
<td>33.4 (11.4)</td>
<td>38.5 (13.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data summarised from<sup>60</sup> and reflects type 3 VWD patients treated with a single 50 IU of VWF:RCo/kg infusion of either recombinant VWF/recombinant FVIII (n=17) at a ratio of 1:3:1 or a plasma derived VWF concentrate (Humate®/Haemate®) (n=15) which contains VWF/FVIII at a ratio of ~2:1. <sup>b</sup>The publication<sup>60</sup> indicates a dose of "5.8 (17.7)" for FVIII, which appears to be an error; the value provided in this table "38.5" is the target dose. <sup>c</sup>The publication<sup>60</sup> indicates a dose of "125.6 (49.0)" for FVIII, which also appears to be an error; the value provided in this Table (i.e. 25) is the target dose. VWF: von Willebrand factor; AUC(0-4): area under the plasma concentration curve from zero to infinity (h·U/dL); Cl: clearance (mL/kg per hour); MRT: mean residence time (hours).
Recombinant VWF therapy for VWD

Table V - Main findings from Phase III human recombinant VWF clinical trial61.

- This trial evaluated the safety and hemostatic efficacy of a rVWF for treatment of bleeds in severe VWD.
- rVWF was initially administered together with rFVIII and subsequently alone, so long as hemostatic FVIII:C levels were maintained.
- Pharmacokinetics (PK) were evaluated in a randomised crossover design (rVWF vs rVWF:rFVIII at 50 IU VWF:RCO/kg).
- Bleed control for all treated bleeds (n=192 bleeds in 22 subjects) was rated excellent (96.9%) or good (3.1%).
- A single infusion was effective in 81.8% of bleeds.
- Treatment success, defined as the number of subjects with a mean efficacy rating of <2.5, was 100%.
- The PK profile of rVWF was not influenced by rFVIII (mean VWF:RCO terminal half-life: 21.9 h for rVWF and 19.6 h for rVWF:rFVIII).
- FVIII:C levels increased rapidly after rVWF alone, with hemostatic levels achieved within 6 hours and sustained through 72 hours post-infusion.
- Eight adverse events (AEs) (6 non-serious in 4 subjects and 2 serious [chest discomfort and increased heart rate, without cardiac symptomatology] concurrently in 1 subject) were associated with rVWF.
- There were no thrombotic events or severe allergic reactions.
- No VWF or FVIII inhibitors, anti-VWF binding antibodies or antibodies against host cell proteins were detected.
- Authors concluded that rVWF was safe and effective in treating bleeds in VWD patients and stabilises endogenous FVIII:C, which may eliminate the need for rFVIII after the first infusion.

VWF: von Willebrand factor; VWD: von Willebrand disease; rFVIII: recombinant factor VIII; rVWF: recombinant von Willebrand factor; IU: International Unit; FVIII:C: factor VIII coagulant activity.

will differ according to regulatory clearances and local suppliers, as will the concentrate properties (e.g. composition, level and functionality of VWF and FVIII).

It is, therefore, likely that the application of biological therapies will change in the future as the concept of personalised therapy is developed. For example, the same factor concentrate is often provided for patients with VWD and those with haemophilia A. Reasons include economical and practical considerations (i.e. cheaper for manufacturers to provide a "one size fits all" solution, easier for clinicians and blood banks to manage a single concentrate product). Restricted access to individual concentrates, due to manufacturer marketing strategies, plasma source, and regulatory restrictions, may also explain this practice.

Although products containing both VWF and FVIII may be clinically efficacious for treating both VWD and haemophilia A, this will not be ideal in all cases. First, there is a potential waste of resources, and second, it could lead to adverse events if not managed carefully during therapy. Thus, giving a patient with VWD, who is expressing defective or deficient VWF but normal FVIII levels, the FVIII in a combined VWF/FVIII concentrate product is wasted and giving a patient with haemophilia A, who is expressing defective or deficient FVIII but normal VWF level and activity, the same combined VWF/FVIII concentrate product is wasteful of the VWF provided in that product. More seriously, giving VWF and FVIII when it is not required (i.e. respectively to haemophilia A and VWD patients) can lead to excess factor levels, and potentially to adverse events such as thrombosis.

On the other hand, there are advantages for selective use of a combined concentrate in some situations, such as in immune tolerance61,63, or for initial therapy.

Individualising patient therapies in von Willebrand disorders

Ideally, a concentrate containing both VWF and FVIII would be initially used in type 3 VWD to boost plasma levels of both VWF and FVIII. After the initial treatment, the patient’s plasma FVIII levels will rise further due to the binding and stabilisation of endogenous FVIII by the exogenously provided (normal) VWF46. This will, therefore, lead to a situation where continued use of a combined VWF/FVIII product will actually generate an excess of plasma FVIII in the patient, increasing the risk for thrombotic events should FVIII levels rise too high. This would theoretically be more likely in concentrates containing a high proportion of FVIII/VWF (see Table II). Thus, it makes good theoretical, clinical (and possibly economic) sense to treat patients with type 3 VWD by a two-pronged approach, and a combined VWF/FVIII concentrate (or rVWF plus rFVIII) initially, and then VWF concentrate (or rVWF) that does not have FVIII thereafter46.

This concept of personalised therapy, employing products selectively containing either VWF or FVIII or both, as specifically required and tailored to individual patients according to the given situation, will continue to develop over time, and the availability of separate rVWF and rFVIII products will facilitate this process. Table VI and Figure 2 provide examples of how this may be applied in the future.

The future of recombinant von Willebrand factor

Recombinant FVIII and recombinant factor IX (rFIX), respectively, have represented the mainstay of treatment of haemophilia A and B now for several years46,65, driven at least in part by the as yet unproven fears of potential infections from modern plasma-based concentrates, and in spite of the debate concerning differential inhibitor formation using some forms of rFVIII vs the plasma-derived FVIII concentrates66,67. rVWF has, in fact, been around for several decades68-70, but has only recently entered into clinical trials. This delay seems to have stemmed from suboptimal cell line selection and initial processing (original lack of co-expression of rFVIII, lack of processing by Furin to remove the pro-VWF polypeptide), fears of potential adverse events (e.g. thrombosis) related to the recognition that rVWF has never been exposed...
Table VI - Towards personalised replacement therapy in von Willebrand disease*.

<table>
<thead>
<tr>
<th>VWD type</th>
<th>Recombinant VWF?</th>
<th>Recombinant FVIII?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>±</td>
<td><strong>Recombinant VWF</strong>: amount required for therapy depends on base-line VWF and reason for therapy (e.g. minor vs major surgery). Recombinant VWF containing all molecular weight forms of VWF might be favoured since this generally reflects the &quot;quantitative loss&quot; in these patients. <strong>Recombinant FVIII</strong>: may only be required if base-line FVIII level is low or for major procedures; possibility of reduction/omission post &quot;steady state&quot; and stabilisation of endogenously produced FVIII.</td>
</tr>
<tr>
<td>2A</td>
<td>+</td>
<td>±</td>
<td><strong>Recombinant VWF</strong>: amount required for therapy depends on extent/type of defect, base-line VWF and reason for therapy (e.g. minor vs major surgery). HMW enriched recombinant VWF might be favoured since this form promotes primary haemostasis best, and generally reflects the 'functional loss' in these patients. <strong>Recombinant FVIII</strong>: may only be required if base-line FVIII level is low or for major procedures; possibility of reduction/omission post &quot;steady state&quot; and stabilisation of endogenously produced FVIII.</td>
</tr>
<tr>
<td>2B</td>
<td>+</td>
<td>±</td>
<td><strong>Recombinant VWF</strong>: amount required for therapy depends on extent/type of defect, base-line VWF and reason for therapy (e.g. minor vs major surgery). HMW enriched recombinant VWF might be favoured since this form promotes primary haemostasis best, and generally reflects the 'functional loss' in these patients. <strong>Recombinant FVIII</strong>: may only be required if base-line FVIII level is low or for major procedures; possibility of reduction/omission post &quot;steady state&quot; and stabilisation of endogenously produced FVIII.</td>
</tr>
<tr>
<td>2M</td>
<td>+</td>
<td>±</td>
<td><strong>Recombinant VWF</strong>: amount required for therapy depends on extent/type of defect, base-line VWF and reason for therapy (e.g. minor vs major surgery); possibility of using lower molecular weight VWF species to facilitate stabilisation of endogenous FVIII and to balance bleeding vs thrombosis risk and to prevent accumulation of HMW VWF. <strong>Recombinant FVIII</strong>: may only be required if base-line FVIII level is low or for major procedures; possibility of reduction/omission post &quot;steady state&quot; and stabilisation of endogenously produced FVIII.</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>(+)</td>
<td><strong>Recombinant VWF</strong>: amount required for therapy depends on reason for, and duration of, therapy (e.g. minor vs major surgery; prophylaxis). Recombinant VWF containing all molecular weight forms of VWF might be favoured since this generally reflects the &quot;quantitative loss&quot; in these patients. <strong>Recombinant FVIII</strong>: will be required for initial infusions; possibility of reduction/omission post &quot;steady state&quot; and stabilisation of endogenously produced FVIII.</td>
</tr>
<tr>
<td>PT</td>
<td>-</td>
<td>-</td>
<td>PT-VWD is a platelet glycoprotein Ib defect and requires platelet transfusion for management of bleeds.</td>
</tr>
</tbody>
</table>

*Table provides the author's suggestive future landscape for personalised therapy in VWD with recombinant VWF and FVIII products. Additional/adjunct therapies will still have a place in management of VWD. Thus, desmopressin therapy will still be useful for managing minor procedures or menorrhagia, etc., especially in type 1 VWD; antifibrinolytics such as tranexamic acid will also be useful in select circumstances. Future therapy in VWD with additional management tools, including recombinant Interleukin 11 and gene therapy can also be anticipated. VWD: von Willebrand disease; VWF: von Willebrand factor; FVIII: factor VIII; HMW: high molecular weight; PT: platelet type.

Figure 2 - Algorithm summarising the author's suggestive future landscape for personalised therapy in von Willebrand disease (VWD) with recombinant VWF and FVIII products. Solid continuous lines indicate the most likely main therapy to be applied in the future landscape of VWD treatment. Dotted lines indicate additional or alternate treatment options depending on extent of VWF and/or FVIII deficiency, reason for treatment and timing of therapy, and according to the concept of "personalised therapy". Refer also to Table VI. VWF: von Willebrand factor; FVIII: factor VIII.
Recombinant VWF therapy for VWD

Finally, just as rFVIII and rFIX products are entering a new phase of extended life products\textsuperscript{77-79}, similar modifications to extend the life of rVWF are also likely to be explored.

Conclusions and future perspectives

Most developed countries currently use "standard" therapy to manage bleeding, using desmopressin wherever possible, VWF/FVIII concentrates in other situations, and additional (e.g. antifibrinolytic) therapy when required. Available concentrates differ in content, for example, in relation to comparative levels of VWF and FVIII, or in the composition of VWF and relative retention or loss of the high molecular weight forms, as well as the labelling of product content (FVIII only vs. FVIII and VWF:RCo), and only selective concentrations are available in different localities according to regulatory clearances and marketing. These reflect important but often over-looked issues when using replacement therapy, and also mean that true global standardisation of biological therapy in VWD is still not feasible. rVWF has been developed and has undergone clinical trials, and this promising therapy may change the landscape of VWD management in the near future. Other manufacturers of VWF concentrate are currently exploring the production of rVWF. It is only a matter of time before patients with VWD can be managed within the concept of personalised medicine rather than a "one size fits all" approach. Whether rVWF, rFVIII, and perhaps other recombinant proteins such as interleukin-11\textsuperscript{80-82} become an armamentarium of recombinants for management of VWD in the future still needs to be determined. The key points from this review are summarised in Table VII.

Table VII - Key points from this review.

-  Congenital von Willebrand Disease (VWD) and acquired von Willebrand Syndrome (AVWS) represent common bleeding disorders, but are also difficult conditions to diagnose and therefore to manage.
-  Both represent von Willebrand factor (VWF) deficiency/defect related disorders and manifest as bleeding disorders due to "functional deficiency of VWF", sometimes also with combined deficiency of factor VIII (FVIII).
-  Use of VWF factor concentrates, often also containing concentrated FVIII, represents the most commonly applied management therapy for VWD/AVWS.
-  As there are significant differences in VWF and/or FVIII content between factor concentrates, and as only select concentrates are available in different localities, the therapeutic management of many treated patients may be non-ideal.
-  Recombinant VWF (rVWF) has been developed and is undergoing clinical trials, and this promising biological therapy may change the VWD management landscape in the near future.
-  In particular, one can envisage the use of rVWF with or without rFVIII, depending on the type of VWD/VWS, as well as the period of treatment, in order to better personalise and optimise therapy.
Note added in proof

rVWF has recently been cleared for clinical use (as the product “Vonvendi”) by the US Food and Drug Administration (refer to: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm476065.htm, and also http://www.vonvendi.com/; accessed on 18/03/2016), for use in adults 18 years of age and older who have VWD. Vonvendi is the first FDA-approved recombinant von Willebrand factor, and is approved for the on-demand (as needed) treatment and control of bleeding episodes in adults diagnosed with VWD.

The Author declares no conflicts of interests.

References


Recombinant VWF therapy for VWD


