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Recombinant VWF: is this the answer for treatment of von Willebrand disease?

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The use of replacement protein factors for treatment of blood clotting disorders has a long history that has involved both major advances and setbacks. Replacement therapies can be viewed as the gold standard treatment for the majority of factor deficiencies and, for certain conditions, such treatments are both highly developed and well established. For the common inherited bleeding disorders, hemophilia A and B, replacement FVIII and FIX concentrate has been in clinical use for many years, with recombinant product prophylaxis now in routine use in those countries that can afford it, and further improvements relating to increasing the half-life of these products at a fairly advanced stage [1].

However, not all factor deficiencies have the same level of development applied to their replacement concentrate therapies. von Willebrand disease (VWD), which results from a qualitative or quantitative deficiency of the multimeric plasma glycoprotein VWF, is a case in point. VWD is a complex disorder with three main subtypes that respond to treatment modalities in fundamentally different ways [2,3,101]. In contrast with hemophilia A, where FVIII replacement therapy is the standard treatment in individuals without complicating factors such as inhibitors, treatment of VWD using other agents such as desmopressin is an effective approach for some subtypes, notably mild type 1 and some mild qualitative type 2 VWD cases in short-term treatment situations. However, in cases where such alternative treatments are contraindicated, and in type 3 and severe type 1 VWD, the use of replacement VWF concentrate for many clinical scenarios is required. Whilst there are several licensed VWF concentrates on the market, their state of development is, in some respects, not as advanced as that for FVIII or FIX replacement therapies. The currently licensed products in use all involve plasma-derived VWF from pools of donors. Whilst current processing techniques to purify these products, as with other available plasma-derived concentrates, mean that the risk of significant viral transmission is currently very low, there are other practical concerns for the clinician who wishes to use these non-recombinant VWF concentrates in real-life treatment scenarios. The majority of licensed concentrates for the management of VWD contain both VWF and FVIII, but the relative proportions of each factor vary markedly, both between different products and batches of the same product, due to differing manufacturing processes that result in variable multimer composition and size distribution [3]. High-molecular weight (HMW) VWF multimers are the most biologically active and with each licensed product containing different amounts, this may be predicted to translate into variable hemostatic potential when administered to the patient. Another complication is the lack of information supplied in some locales relating specifically to VWF activity

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within the product, with only the FVIII level being stated. This means that dosage for a given concentrate may be based on the FVIII level, determined via the FVIII coagulant (FVIII:C) assay rather than via more direct measurements relating to VWF activity. In some locales, products do include VWF activity information (e.g., ristocetin cofactor [VWF:RCo] assay information) and dosage for individual concentrates is based on VWF:RCo levels relative to FVIII:C levels [4]. This variation in labeling and practice reflects the development of products that were originally licensed for use in the treatment of hemophilia A and pre-dates subsequent developments relating to VWF activity measurement that have not yet been approved by regulatory authorities. Whilst this treatment monitoring approach is valid for a given concentrate, as the FVIII level post-treatment will reflect the VWF level and, in turn, the corresponding VWF activity level for that particular product, it does not provide a means of measuring direct intra-product VWF function, as the correlation between FVIII and VWF will vary markedly between different products [3]. A further complication when monitoring treatment with VWF concentrate in type 3 VWD via this route is that the level of FVIII will rise over and above that contributed by the concentrate due to the stabilization of endogenous FVIII. It has been recommended that, in prolonged VWF replacement therapy, FVIII levels should be monitored and treatment adjusted to avoid unacceptably high levels [5,101]; although, a recent systematic review of prospective studies indicates that the risk of thrombotic adverse events in hemophilia and VWD factor replacement is small [6].

Such complications do not allow for a more standardized approach in the use of VWF concentrate in a range of clinical scenarios, and may mean VWF concentrate require closer monitoring during treatment episodes, although in reality, levels are likely to be maintained at a level above that strictly needed for the required hemostatic response, as recommended by various national guidelines [7]. However, given that this patient group have either a quantitative or qualitative deficiency of VWF, this situation is not ideal and any replacement therapy should be designed in such a way as to ensure a specific, rapid and optimal response that is easily monitored and mirrors available best practice guidance for management of treatment episodes as closely as possible.

The development of recombinant VWF concentrate promises to change this situation. The limitations associated with the consistency of available plasma-derived VWF products, and reliance on a donor pool with potential future viral threat, would be circumvented. The feasibility of biologically functional recombinant VWF has been demonstrated [8], and a commercially developed product has been undergoing clinical trials designed to assess the pharmacokinetics of recombinant VWF:recombinant FVIII and recombinant VWF, and to assess the safety and efficacy of recombinant VWF:recombinant FVIII and recombinant VWF, in the treatment of bleeding events in subjects with severe forms of VWD [9,102]. The recombinant VWF, purported to be the largest recombinant protein yet manufactured, is co-expressed with recombinant FVIII in CHO cells. Subsequent processing steps, including exposure to recombinant furin in order to remove the VWF pro-polypeptide, result in a product that is both plasma and albumin free. In addition, the assembled recombinant VWF multimers have not been exposed to the metalloprotease ADAMTS-13, leading to a population comprising a significant proportion of ultra-HMW multimers [10]. This manufacturing pipeline should allow the production of recombinant VWF with consistent properties between each batch process, although it has raised concerns that administration of ultra-HMW multimers may increase thrombogenic potential. In response to this concern, further animal studies have been undertaken to demonstrate safety [10,11]. Dependant on the positive outcome of human trials [102], recombinant VWF should be available in the near future for use in a clinical setting.

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So, will the advent of recombinant VWF-based therapy for VWD lead to improved management of the disorder? The answer is a qualified 'yes'. Current approaches, utilizing desmopressin, antifibrinolytics and/or plasma-derived concentrates are well understood, are either very or reasonably cost effective, and are unlikely to be swept away on a tide of recombinant therapy. However, the advent of recombinant VWF concentrate will widen treatment options and, in selected individuals, should permit more appropriate management of their bleeding disorder. Whilst promising to introduce more consistency to VWF concentrate production and subsequent management of VWD, recombinant VWF will bring its own set of issues to be resolved in a clinical context. At the moment it remains unclear as to how these products will be implemented. Will they take the form of recombinant-only VWF or will they be administered as combined products that include recombinant FVIII? In type 3 VWD, a combined VWF–FVIII recombinant product

would be required on commencement of a treatment episode in order to achieve therapeutic levels of both factors and optimal response. However, the presence of recombinant VWF in the circulation will then stabilize endogenous FVIII in the patient, leading to a possible excess of this factor with potential for increased thrombotic events [3,12]. This would suggest that two formulations of the product would be required, with a switch to a recombinant VWF-only product being administered once both VWF and FVIII levels were in the therapeutic range.

In conclusion, there is a wealth of experience using existing intermediate and, more recently, higher purity plasma-derived VWF concentrates [13–15], despite the limitations associated with these products discussed above. Recombinant VWF concentrate is likely to be adopted as an adjunct to therapeutic options for the treatment of VWD for the foreseeable future. It should also be remembered that the quality of treatment in VWD varies across the globe, with some areas having access to limited or no concentrates. This, allied with the increased expense of recombinant products, may limit or delay their adoption into clinical practice on a wider basis. However, it is reasonable to expect, as has happened with hemophilia A and B, that the treatment of VWD will evolve further over time to include more routine use of prophylaxis and a switch to recombinant products, where both clinical indicators and economic considerations permit. This process should result in a more standardized approach to VWD management over time.

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