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Prophylaxis in von Willebrand Disease: Coming of age?

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Summary

Although in most cases von Willebrand Disease (VWD) is a mild disorder, a subgroup of patients experience frequent bleeding. In contrast to severe haemophilia where prophylaxis is the accepted standard of care, this is less frequently used in VWD. Most type 1 VWD patients can be adequately managed with episodic desmopressin and tranexamic acid. In patients with more severe disease, especially those with type 3 VWD, joint bleeds, epistaxis, menorrhagia and gastrointestinal bleeding are problematic and usually require treatment with von Willebrand Factor (VWF/FVIII) concentrate. Whilst in the past these patients were managed with on demand VWF/FVIII concentrate, several recent reports have demonstrated the value of prophylactic treatment. Despite some uncertainties about the economic impact of treatment of severe VWD, prophylaxis with VWF concentrate should now be considered as the standard of care for the more severe end of the spectrum of affected individuals. The recent introduction of recombinant VWF concentrate is likely to improve the acceptability of prophylaxis.

Introduction

Haemophilia and von Willebrand disease (VWD) due to deficiency of FVIII/IX and von Willebrand factor (VWF) respectively, comprise the most common inherited bleeding disorders. Despite the obvious differences in mode of inheritance and pathophysiology, they share a number of characteristics. As with all the inherited bleeding disorders, there is a direct relationship between the severity of the factor deficiency and the symptoms of disease and correction of the deficiency stops and prevents bleeding.

VWD is caused by abnormalities in the *VWF* gene on chromosome 12, with an autosomal dominant or recessive inheritance pattern (1). Although VWD is the most common inherited bleeding disorder, most diagnosed individuals have mild disease (2). Typical symptoms are those of mucosal bleeding including epistaxis, menorrhagia, as well as skin bruising and bleeding after surgery and dental extractions. Treatment of VWD is primarily conducted with tranexamic acid, desmopressin or VWF/FVIII concentrate, which are given to stop bleeding or prevent bleeding in the context of surgery. In contrast to the situation in haemophilia, the use of long-term prophylaxis is less well developed in VWD.

Haemophilia is inherited in a sex-linked manner and largely affects males, although some female carriers can have reduced levels and also be symptomatic. Typical symptoms are joint and muscle bleeding as well as internal bleeding, and bleeding after surgery and invasive procedures. There is an inverse relationship between residual factor level and severity of bleeding. Individuals with severe (<1% FVIII/IX) disease experience frequent spontaneous joint bleeds and develop

arthropathy whilst persons with moderate (1% to <5% FVIII/IX) disease experience joint bleeds less frequently and rarely develop severe arthropathy (5-6). This observation led to the suggestion that if you could administer regular FVIII/IX to always have a level above 1% then it should be possible to reduce the number of joint bleeds and convert the phenotype of patients with severe disease to that of moderate/mild individuals.

Haemophilia and prophylaxis

A five-decade clinical experience, starting in Sweden (3-4) has established prophylaxis using regular infusions of factor concentrate as the treatment of choice in children with severe haemophilia.

Data supporting the benefits of prophylaxis in haemophilic patients largely come from retrospective or non-controlled studies. The different cohorts of patients described in the Malmo experience (3) and in other studies in the following years (7-9) evaluated short-term outcome such as frequency of joint bleeds, or long-term clinical outcome such as arthropathy (10-11). Clinical and radiological scores demonstrated that signs of arthropathy were not detectable in children starting prophylaxis before two years of age (8), or showing that only younger children receiving higher doses earlier in life did not develop any bleeding episode (3). In some of these studies other medical and social implications on patients' Quality of Life (QoL) were also investigated (e.g., number of hospital visits and hospitalisations, number of school/work days lost).

Despite the long clinical experience and extensive use of prophylaxis in this setting, a Cochrane review in 2006 concluded that evidence supporting clinical

benefits of prophylaxis over on-demand therapy was insufficient (12). In the last decade, however, several randomized-controlled studies (13-14) have definitively confirmed primary prophylaxis as the gold standard of care in severe hemophilia, and national guidelines in several countries now advise commencing early prophylaxis (15-16).

Current prophylaxis regimens do not completely prevent joint disease (13). In the last few years, more intensive prophylaxis regimens have been explored (17), achieving almost zero joint bleeds. To get the best outcomes with the available resources, individualization of therapy is applied, which considers the individual's bleeding pattern, condition of their musculoskeletal system, level of physical activity and the pharmacokinetic profile of the clotting factor concentrate used (18-22).

In order to optimize therapeutic regimens related to outcomes, several studies suggested starting with a once-weekly regimen (23-24).

Von Willebrand Disease

Although VWD is more prevalent than haemophilia, less evidence is available on its optimal management, probably due to the lesser number of patients with severe disease. In the International Society on Thrombosis and Hemostasis (ISTH) classification, different VWD types are recognized depending on the quantitative (types 1 or 3) or qualitative (type 2) deficiency that includes four sub-types: 2A, 2B, 2M and 2N (25).

The clinical VWD manifestations are mucocutaneous bleeding and prolonged oozing after surgical or invasive procedures. Menorrhagia may be the only clinical manifestation. Soft tissue and joint bleeds are rare, except in Type 3 VWD. The

severity of the bleeding tendency is usually proportional to the degree of the primary deficiency of VWF and to the secondary deficiency of FVIII. The expression of the disease is mild in most patients with type 1, and more severe in some type 2 and particularly in type 3 VWD. Several attempts have recently been made to evaluate sensitivity and specificity of bleeding symptom in VWD diagnosis. A bleeding severity score has now been developed to aid the diagnosis of VWD (26).

Management of VWD includes the prevention or treatment of bleeding by correcting the primary haemostatic defect and the coagulation defect due to FVIII deficiency (27-28). Correction of both deficiencies and raising endogenous VWF levels can be achieved by administering the synthetic peptide desmopressin (deamino-8-D-arginine vasopressin; DDAVP) or, in unresponsive patients, plasma-derived VWF/FVIII or VWF concentrates devoid of FVIII (28-31). Antifibrinolytic agents such as tranexamic and epsilon aminocaproic acid, platelet concentrates and combined estrogen-progestogen drugs can be co-administered (32).

Prevention of bleeding is achieved by prophylaxis, which can be performed in case of surgery or invasive procedures (short-term) or, in the severe forms of VWD, to prevent recurrent bleeding episodes (long-term prophylaxis).

Short-term prophylaxis for surgery

The choice of the best treatment regimen before surgery in patients with VWD depends on type of VWD, type of surgery, baseline VWF and FVIII levels, response to DDAVP and its potential side-effects. Table 1 show Italian guidelines for prophylaxis before surgery (28); substantially similar advice is given in the UK and USA Guidelines (33,34).

Desmopressin (DDAVP) is the first-choice option for patients with Type 1 VWD and baseline VWF and FVIII levels higher than 10 U/dL (35). Type 2 patients have a highly variable pattern of response to DDAVP which is better in type 2M than in Type 2A (36). In Type 2B, DDAVP remains controversial because of the potentially transient appearance or aggravation of thrombocytopenia, which could increase bleeding. Patients with type 3 VWD are always unresponsive to DDAVP. In type 2N VWD associated with homozygous or heterozygous R854Q, DDAVP is usually able to correct FVIII deficiency, although its half-life may be relatively short (35, 37). In patients with isolated collagen-binding defects, desmopressin improves all VWF/FVIII measurements including VWF:CBA, albeit with a persistent discrepancy of VWF:CBA/VWF:Ag ratio(36,38).

A test infusion of DDAVP (0.3 micrograms/kg) is recommended to establish the individual response pattern and to plan its appropriate use, because of the variability in response to DDAVP between patients, which reasons are not clear. Furthermore, patients treated repeatedly with DDAVP may become less responsive, probably because stores are exhausted. The average factor VIII responses obtained if DDAVP is repeated at 24 -hours intervals are approximately 30% less than then obtained after the first dose, with a consequent limitation of the use of DDAVP when Factor VIII levels must be maintained above the baseline levels for a prolonged period of time, as in major surgery.

In VWD patients in whom DDAVP is not appropriate due to inadequate response or contraindication, and in patients undergoing major surgery, treatment with virally-inactivated plasma-derived concentrate is recommended (30,39). Table 2 shows the VWF/FVIII products licensed in Europe for the treatment of VWD. Many studies

documented the efficacy of VWF/FVIII concentrates as prophylaxis of bleeding in VWD patients undergoing surgery or invasive procedures (40-48).

The recent literature shows that the best management of VWD undergoing surgery includes a pharmacokinetic study to tailor the loading and maintenance doses of VWF/FVIII concentrates for each patient (49). This is particularly important considering the heterogeneous nature of VWD and plasma derived concentrates. The same studies also underscore that, along with VWF levels, FVIII levels should be monitored daily in the postoperative period in order to prevent exposure to high FVIII levels, which can increase the thrombotic risk. Therefore, primary prophylaxis with low molecular weight heparin at the same dosages and schedules used in the general population, are recommended in VWD patients undergoing major surgery or procedures at high risk of venous thromboembolism (50). In this regard, there is a growing interest in replacement therapy with VWF concentrates almost devoid of FVIII (Wilfactin®). The same considerations are applicable for long-term secondary prophylaxis, particularly in patients with cardiovascular/thromboembolic risk factors. Recently recombinant VWF concentrate has been licensed in the USA. Safety and pharmacokinetics (PK) of recombinant von Willebrand factor (rVWF) combined at a fixed ratio with recombinant factor VIII (rFVIII) were recently reported in a prospective phase 1, multicenter, randomized clinical trial. rVWF was well tolerated and no thrombotic events, inhibitors, or serious adverse events were observed (51).

Bleeding phenotype in VWD

Clinically, the leading symptom in VWD is bleeding, chiefly of mucosal origin. In the most severe forms of VWD, especially type 3, joint and muscle bleeding

resembling that seen in moderate haemophilia A may also be observed. Type 1 VWD typically manifests with mild mucocutaneous bleeding but symptoms can be more severe when VWF levels are lower than 15 IU/dL. Epistaxis and bruising are common symptoms among children, frequently and severely enough to cause anemia. Epistaxis also often occurs in type 2A, 2B and 2M VWD. Severe epistaxis causes interference or distress with daily or social activities, and impacts in QoL of patients (52,53).

Most cases of epistaxis can be managed with conservative techniques, but in some cases, cauterization (chemical or electrical) or nasal packing is required. In rare cases, surgical cauterization or sphenopalatine artery ligation or embolization is necessary to control severe epistaxis.

Type 2 A and type 3 VWD patients often experience other symptoms such menorrhagia as and GI bleeding due to angiodysplasia or unlinked to a vascular lesions. Menorrhagia is the most common finding in women of reproductive age (54-56). Objectively, menorrhagia is defined as bleeding that lasts for more than seven days or results in the loss of more than 80 ml of blood per menstrual cycle. Treatment of menorrhagia in women with inherited bleeding disorders should be individualized. Available treatments include hormonal therapy (oral contraceptives, depot medroxyprogesterone acetate, danazol, GnRH analogs) or local treatments (levonorgestrel-releasing Mirena coil) and non-hormonal therapy such as desmopressin, and tranexamic acid. For women who have completed their family endometrial ablation is another highly effective option. Patients are often non-responsive to the above treatments and may require VWF/FVIII replacement therapy to stop or prevent the heavy bleeding.

Postpartum hemorrhage (PPH) remains one of the leading causes of maternal morbidity and mortality worldwide and is a problem for type 3 and some 2A VWD women where the endogenous FVIII/VWF does not normalize with pregnancy. A treatment algorithm for severe persistent PPH has been developed, including mechanical or surgical maneuvers such as intrauterine balloon tamponade or hemostatic brace sutures with hysterectomy as the final surgical option for uncontrollable PPH. Pharmacologic options include hemostatic agents such as tranexamic acid, with timely transfusion of blood and plasma products playing an important role in persistent and severe PPH (57).

Gastrointestinal bleeding associated with angiodysplasia, is a challenging complication in mostly elderly individuals where surgical treatment is often not feasible. Angiodysplasia is a vascular malformation and is associated with both inherited and acquired VWD (58-59). In inherited VWD it is seen particularly in patients lacking high-molecular-weight (HMW) multimers (type 2 and type 3). In acquired VWD it is often seen in Hayde's syndrome associated with aortic stenosis where the loss of HMW multimers plays a role in the pathogenesis of the acquired VWD (58). Affected patients may need to be hospitalized for long periods of time and often require several weeks of treatment leading to high costs and poor quality of life. Due to its tendency of recurrence, angiodysplasia-associated with gastrointestinal bleeding is an indication for secondary long-term prophylaxis (58). The von Willebrand Disease Prophylaxis Network (VWD PN) reported that GI bleeding was the most common reason for initiation of prophylaxis in adults (34%) (61). A number of alternative therapeutic measures have been attempted in the last few years in the management of recurrent gastrointestinal bleeding in VWD (62).

Oestrogens, progestogens and the somatostatin analogue octreotide have been tried, but from the little available data it is not possible to obtain solid conclusions on their effectiveness. More recently, interest has been focused on the use of drugs with angiostatic properties, such as thalidomide, but few case reports are available, reporting an improved clinical picture and the reduction of the transfusion requirement (63,64). A positive effect on refractory gastrointestinal bleeding in two patients with VWD has also been reported with atorvastatin, that has anti-angiogenic properties when administered at very large doses (up to 80 mg daily) (65,66).

Finally, type 3 VWD is characterized by the most severe haemophilia-like bleeding phenotype (67). Particularly in this setting of patients it is logical to translate the success of prophylaxis in haemophilia to severe VWD. Prophylaxis can be implemented early in life in a home setting, and prevention of bleeding and its consequences is possible.

Long-term prophylaxis

Patients with severe forms of VWD may present a severe bleeding phenotype, and in these patients secondary long-term prophylaxis with VWF/FVIII concentrate may represent the optimal therapy rather than on-demand treatment on the occasion of bleeding episodes. However, some differences must be considered between VWD and haemophilic patients regarding treatment. Firstly the differential pharmacokinetic behavior of VWF and FVIII, since it is known that infusion of VWF/FVIII concentrates in patients with severe VWD with very low levels of FVIII

induces an immediate rise of FVIII levels (68), followed by a secondary rise due to binding and stabilization of endogenous FVIII to the infused VWF. The content of FVIII and VWF vary widely among licensed products (30) and different profiles may be obtained after infusion. The second important difference is the variability of the bleeding phenotype among VWD patients, as well as the hemostatic response to concentrates, variable according to type of bleed (mucosal or joint bleeds).

The first “large” experience on the efficacy of secondary prophylaxis in VWD was gained in Sweden in 35 patients with severe VWD (69). The investigators concluded that long-term prophylaxis is warranted in the majority of cases with type 3, and in some cases with other types of VWD resulting in a substantial decrease in the annual number of bleeding events. The population investigated was mostly type 3 VWD patients, with a median age at start of prophylaxis of 13 years. The predominant indications for prophylaxis were nose, mouth and joint bleeds. The number of bleeds was significantly reduced after prophylaxis and children starting prophylaxis before 5 years of age never developed arthropathy. Secondary prophylaxis was also retrospectively evaluated in a subgroup of a cohort of 100 Italian VWD patients (70), 71% of whom had VWF:RCo levels <10IU/dL. Among the 100 patients, 11 underwent 17 episodes of long-term secondary prophylaxis to prevent recurrent bleeding at the same site (mostly gastrointestinal and joint bleeding). The clinical responses were rated as excellent or good in 100% of cases, with a significant reduction in annual consumption of concentrate, number of transfused blood units and number of days spent in hospital. During the 4358 days of prophylaxis (median 201, range 30-730) only four bleeding episodes were observed. Similar results of excellent efficacy were reported in a larger cohort, with

32 long-term prophylaxis applied in children, adolescent and young adults with VWD; recurrent bleeding stopped in 31 patients, the monthly bleeding frequency and the bleeding score was significantly reduced compared to the pre-prophylaxis rate but one patient developed inhibitor (71). Each of these three studies were retrospective and involved a relatively small number of patients.

In 2008 an international study group, the VWD PN was established to study the role of prophylaxis in VWD; 74 centres from around the world participated. The first network-sponsored survey by the centres showed that the use of prophylaxis was rare in type 1 and 2 VWD patients but was most common in type 3 disease. Prophylaxis was given to prevent joint bleeding (40%), epistaxis/oral bleeding (23%), gastrointestinal bleeding (14%) and menorrhagia (5%) (72).

Between 2008 and 2011, the VWD International Prophylaxis (VIP) study was conducted by the network and which contained both retrospective and prospective components; the aims were to retrospectively evaluate the effect of prophylaxis on bleeding frequency and prospectively confirm the efficacy and address issues of cost-effectiveness and quality of life. The main conclusion of the retrospective analysis was the efficacy of prophylactic treatment, particularly in FVIII-dependent haemorrhages. Differences in annualized bleeding rates within individuals (during prophylaxis vs before prophylaxis) were significant for the total group ($P < 0.0001$), and for those with primary indications of epistaxis ($P = 0.0005$), joint bleeding ($P = 0.002$) and GI bleeding ($P = 0.001$). The limitations of this study include the retrospective design and the fact that the inclusion criteria (prophylaxis for at least 6 months and demonstrated compliance) may represent a bias by removing from observation patients for whom prophylactic regimen was abandoned because of

lack of success or acceptability. The prospective study evaluated the effect of prophylaxis in a treatment escalation study design (73). However, only 11 patients completed the protocol, and this is a major limitation of the observation. The aim of the study was to establish the optimal treatment regimens for the most common bleeding conditions in clinically severe VWD, but the statistical power of the population was insufficient for this evaluation. The results showed that the use of prophylaxis with appropriate stepwise dose escalation decreased the median annualized bleeding rate from 25 to 6.1 (CI of the rate difference: -51.6, -1.7) and the median annualized bleeding rate was even lower (4.0; CI: -57.5, -5.3) when the subjects reached their final dosing level.

With the objective of investigating the response to prophylaxis, focusing on specific bleeding type, a recent analysis was conducted combining data from the retrospective and prospective VIP study, and analyzing a cohort of 105 subjects (74). The authors concluded that institution of regular replacement therapy has a dramatic effect on bleeding frequency but does not change the proportions of type of bleeds that occur to a great extent. There is variation among patients with regard to response to therapy, both among and within subtypes of VWD. GI bleeding stands out as having a lower response to prophylaxis than other bleeding sites and requiring more frequent prophylactic infusions. It was also noted that when the treatment frequency is escalated for joint bleeding, higher doses were used.

Table 3 shows the studies reporting on the use of long-term prophylaxis in VWD. Although clinical experience with VWD/FVIII prophylaxis has been rated as satisfactory, some uncertainties persist such as the optimal dose of concentrate and

the regimen for prophylaxis, due to the wide heterogeneity of the bleeding tendency that impacts heavily on QoL.

CONCLUSION/FUTURE Perspectives

A selected population of VWF with severe bleeding phenotype may benefit from long-term prophylaxis with VWF concentrate. The standardization and validation of the Bleeding Score (75), and its application to evaluate the patients' tendency to bleed (76-78) will likely aid individualizing therapy.

In contrast to haemophilia, pharmacoeconomic analysis to assess the economic impact of treatment of severe VWD, comparing on demand versus prophylactic regimens are still lacking. A recent Italian cost-analysis on long-term prophylaxis in VWD in the Italian context (79) showed (with some limitations due to the single case reports used for the analysis) that long-term prophylaxis with VWF with a low FVIII content is likely to be a cost-effective approach with a favorable impact on the reduction of health care resource consumption and with the improvement in the QoL of the patients. However, more prospective trials are needed to evaluate the cost-effectiveness and the improvement on a patient's QoL of long-term prophylaxis. VWF produced by recombinant technology could offer an additional option for the treatment of VWD by eliminating infective risks associated with plasma products. It is now time to seriously consider prophylaxis for severe VWD as a standard of care rather than novelty.

Table 1

Evidence-based recommendations for surgery prophylaxis in von Willebrand disease.

Autologous replacement therapy (DDAVP)
Surgical or invasive procedures should be covered with DDAVP in responsive patients unless contraindicated
A DDAVP test infusion measuring FVIII:C and VWF:RCo levels at 1 hour (peak) and 4 hour (clearance) is recommended before the clinical use of the drug, owing to within-patients consistency in response
In type 1 with baseline VWF:RCo and FVIII:C levels >10U/dL, DDAVP is usually an effective treatment
In type 2A, DDAVP may be used if a test infusion indicates an adequate response
In Type 2B, DDAVP is contraindicated
In Type 2M, DDAVP may be used if a test infusion indicates response
In Type 2N, DDAVP may be effective but the half-life of FVIII is shortened
In Type 3, DDAVP is ineffective
Allogenic replacement therapy (VWF/FVIII or VWF concentrates)
Patients unresponsive to DDAVP or in whom DDAVP is contraindicated, should be treated with virus-inactivated plasma-derived VWF/FVIII concentrates
Prophylaxis for major surgery: daily doses of 50 IU/kg of VWF/FVIII to maintain FVIII:C level >50 U/dL until healing is complete (usually 5-10 days)*
Prophylaxis for minor surgery: daily or every other day doses of 30-60 IU/Kg of VWF/FVIII to maintain FVIII:C level >30 U/dL until healing is complete (usually 2-4 days)*
Prophylaxis for dental extractions or invasive procedures: single dose of 30 IU/Kg of VWF/FVIII to maintain FVIII:C level >50 U/dL for 12 hours*
Measure plasma levels of FVIII:C and VWF:RCo every 12 hours on the day of surgery, then every 24 hours
A dosing pharmacokinetic study should be considered before major surgery, particularly for type 3 VWD patients

*these dosages are indicated for VWD patients with severely reduced FVIII:C/VWF:RCo levels (less than 10 U/dL).

Adapted from Mannucci et al, Blood Transfus 2009; 7: 117-126

Table 2.**VWF/FVIII products licensed for the treatment of von Willebrand disease.**

Product	Manufacturer	Purification	Viral inactivation	VWF:RCo/Ag (ratio)	VWF:RCo/FVIII (ratio)
Alphanate	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72h)	0.47 + 0.1	0.91 + 0.2
Factor 8Y	BioProducts Laboratory	Heparin/glycine precipitation	Dry heat (80°C, 72h)	0.29	0.81
Fandhi	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72h)	0.47 + 0.1	1.04 + 0.1
Haemate P	CSL Behring	Multiple precipitation	Pasteurization (60°C, 10h)	0.59 + 0.1	2.45 + 0.3
Immunate	Baxter	Ion exchange chromatography	S/D + vapor heat (60°C, 10 h)	0.47	1.1
Wilate	Octapharma	Ion exchange + size exclusion chromatography	S/D + dry heat (100°C, 72h)	-	0.9
Wilfactin	LFB	Ion exchange + affinity	S/D, 35 nm filtration, dry heat (80°C, 72 h)	≈ 0.95	≈ 50
Vocento	CSL Behring	Multiple precipitation + albumin ligand chromatography	S/D + Dry heat	-	2.4

VWF: von Willebrand factor; RCo: ristocetin co-factor; Ag: antigen; FVIII: factor VIII; S/D: solvent/detergent;

D: detergent ; ≈: approximately

Adapted from Castaman G, Haematologica 2013; 98: 667-674.

Table 3**Studies reporting on the use of long-term prophylaxis in VWD**

Author, year Design, Reference citation	Patients	Median age at start of prophylaxis	Median time on prophylaxis	Type of VWD	Primary bleeding indication	Main results
Berntorp, 2005 Retrospective	37	13 (1-61)	11 years (2-45)	Type 3: 28 Type 2: 6 Type 1: 3	Mucocutaneous bleeds and joint bleeds	Number of bleeds reduced after prophylaxis. No arthropathy in children starting prophylaxis before 5 years of age.
Federici AB, 2007 Retrospective	11	-	-	Type 3: 5 Type 2A: 4 Type 2M: 1 Type 1: 1	GI bleeding: 7 Joint bleeding: 4	Clinical responses excellent or good in 100% of cases. Significant reduction of annual consumption of concentrates, n. of transfused blood units and n. of days spent in hospital.
Halimeh S, 2011 Retrospective	32	Children: 13 Adolescents: 7 Adults: 12	3 years	Type 1: 4 Type 2: 15 Type 3: 13	-	Recurrent bleeding stopped in 31 patients. Monthly bleeding frequency significantly reduced (p<0.001)
Abshire T, 2013 Retrospective	59	22,4 (2.3-7.2)	2.2 years	Type 3: 34 Type 2A: 10 Type 2B: 8 Type 2M: 2 Type 1: 5	GI bleeding: 13 Epistaxis: 13 Joint bleeding: 12	Significant reduction in median within- individual n. of bleeds/year (p<0,0001)
Abshire T, 2015 Prospective	11	34.6 (3-80.6)	-	Type 3: 54 Type 2A: 25 Type 2B: 9 Type 2M: 3 Type 2 unk: 1 Type 1: 13	Epistaxis: 6 GI bleeding: 3 Joint bleeding: 2	Median annualized bleeding score from 35 to 6.1 (95% C.I.:51.6 to 1.7)
Holm E, 2015 Prospective and retrospective ⁽⁷⁴⁾	95 retr. 11 prosp.	Mean: 26 (1- 81)	-	-	Adults: GI bleeding 34% Joint bleeding 20.8% Children: Epistaxis 43.2% Joint bleeding 31.8%	Significant median reduction in bleeding, within individuals, for epistaxis (p<0,0001), GI bleeding (p<0,0003), joint bleeding (p<0,0001) and menorrhagia (p=0.008)
Miesbach W, 2015 ⁽⁸⁰⁾ Retrospective	3	-	-	Type 3: 2 Type 2A: 1	GI bleeding	Resolution of GI bleeding in 2 of the 3 patients

Khair K, 2015 ⁽⁸¹⁾ Retrospective	4	Mean age: 6.8	-	Type 3: 4	GI bleeding: 1 Joint bleeding: 3	No bleeding during prophylaxis
Batty P, 2014 ⁽⁸²⁾ Retrospective	8 Home treatment: 4 regular prophylaxis 2 on demand 1 targeted prophylaxis 1 intermittent prophylaxis on demand	Adults >18 years	-	-	-	Efficacy rated as excellent or good in 96% cases. No treatment failure.
Nowal-Gottl U, 2013 ⁽⁸³⁾ Prospective	15 tot (prophylaxis on demand, surgical procedures)	Children <6 years	-	-	-	Efficacy rated as excellent or good in 99.7% cases. No inhibitors development. No thromboembolic events.
Castaman G, 2013 ⁽⁸⁴⁾ Prospective	31 patients-secondary long term prophylaxis	-	-	Type 1: 9 Type 2A: 1 Type 2B: 5 Type 3: 16	Joint bleeding (41 events) GI bleeding (34 events) Menorrhagia (17 events)	Good to excellent response in 92.9% cases; Moderate and poor in 6.3 % cases
Howman R, 2011 ⁽⁸⁵⁾ Retrospective	2	-	-	Type 3: 2	-	Prevention of bleeding in 1 patient. Poor response and inhibitor development in 1 patients.

* Not a primary study – it includes patients from other studies on this table

Prophy=prophylaxis

n.=number

retr.=retrospective

prosp.=prospective

tot.=total

on dem. = on demand

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