Review Article

Treatment Options in Hemophilia

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Summary

Background: Approximately 4550 persons were under treatment for hemophilia in Germany in 2017. The condition is currently treated with intravenous supplementation of the missing clotting factor, either prophylactically or as needed. Newer treatment options rely on novel mechanisms of action.

Methods: This review is based on pertinent publications retrieved by a selective search in MEDLINE/PubMed, as well as on expert opinions and the recommendations of specialty societies.

Results: Randomized controlled trials have shown that, in children aged 30 months to 6 years, prophylactic clotting-factor supplementation yields a markedly lower annual rate of hemorrhage than supplementation as needed: 3.27 (standard deviation [SD] 6.24) for the former vs. 17.69 (SD 9.25) for the latter. A similar large effect was seen in patients aged 12 to 50 years, with hemorrhage rates of 1.9 (SD 4.1) vs. 28.7 (SD 18.8). Clotting-factor preparations with longer half-lives make it possible to lessen the frequency of administration and to prevent subtherapeutic factor levels. A number of alternatives to clotting-factor supplementation have recently been approved or are currently being clinically tested. These new drugs are injected subcutaneously and have a longer half-life, possibly enabling better protection against bleeding than the current standard treatment. A further advantage of some of these drugs is that they can be given even in the presence of inhibitors to factor VIII. In addition, initial (phase I) clinical trials of gene therapy have been performed successfully for both hemophilia A and hemophilia B.

Conclusion: Now that new alternatives to classic supplementation therapy are becoming available, pertinent treatment algorithms for patients with hemophilia will have to be developed. It is still unclear to what extent the new drugs might supplant clotting factor supplementation as the first line of treatment.

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Hemophilia is an X-linked, recessively inherited coagulation disorder entailing a lack of coagulation factor VIII, FVIII (hemophilia A) or coagulation factor IX, FIX (hemophilia B). In its latest annual report, the World Federation of Hemophilia (WFH) states that worldwide 196 706 patients are recorded as having hemophilia, and that 80 to 85% of these have hemophilia A (e1). In 2017 there were approximately 4550 hemophilia patients receiving treatment in Germany (e1).

The severity of hemophilia and of its clinical symptoms is determined by residual FVIII or FIX activity as measured in the blood. According to the extent to which coagulation factor levels are reduced in laboratory tests, cases are divided into severe (factor level less than 1%), moderate (factor level 1 to 5%), and mild (factor level 5 to 40%) hemophilia, as residual activity affects the hemorrhage risk (1). While patients with untreated severe hemophilia may have up to 60 hemorrhages per year, this figure is often less than one hemorrhage per year in mild hemophilia (1). However, there is often no clinical difference between moderate and severe hemophilia (e2).

The gold standard for hemophilia treatment has for many years been regular, long-term treatment to prevent hemorrhage (prophylaxis), consisting of infusions of plasma-derived or recombinant factor drugs. The aim is to minimize the number of spontaneous hemarthroses. Additional infusions are performed in cases of breakthrough bleeding, following traumatic injuries, and before sporting activities or surgeries.

The most common complication of treatment for severe hemophilia is the development of inhibitors (inhibitor hemophilia). This occurs in approximately 30% of patients and is particularly common during the initial treatment period in early childhood. It is more widespread in hemophilia A than in hemophilia B (2). In such cases coagulation factor replacement has almost no effect and bypass drugs such as activated prothrombin complex concentrate or recombinant activated coagulation factor FVII (rFVIIa) are used instead. In approximately 80% of patients, immune tolerance therapy consisting of regular, high-dose coagulation factor infusions administered over a long period eliminates inhibitors (3). The risk of developing inhibitors is affected by multiple factors (2). The importance of selecting plasma or recombinant factor concentrate for this use is a subject of controversy (4, 5).

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TABLE 1

Hemorrhage rates during prophylactic treatment with extended half-life factor concentrates

Drug, indication	Trial, no. of participants	Dose, frequency of administration	Median annual hemorrhage rate (IQR)
Damoctocog alfa pegol HA	PROTECT FVIII (17) (<i>n</i> = 114)	30 to 40 IU/kg twice per week 45 to 60 IU/kg every 5 days 60 IU/kg once per week	1.9 (0 to 5.2) 1.9 (0 to 4.2) 0.96 (0 to 4.3)
Efmoroctocog alfa HA	A-Long (18) (<i>n</i> = 165)	25 to 65 IU/kg every 3 to 5 days 65 IU/kg once per week	1.6 (0.0 to 4.7) 3.6 (1.9 to 8.4)
Ruriotocog alfa pegol HA	Prolong-ATE (19) (<i>n</i> = 120)	45 ± 5 IU/kg twice per week	1.9 (0.0 to 5.8)
Turoctocog alfa pegol HA	Pathfinder (20) (<i>n</i> = 175)	50 IU/kg every 4 days	1.33 (0.0 to 4.61)
Albutrepenonacog alfa HB	PROLONG-9FP (21) (<i>n</i> = 63)	40 IU/kg once per week 75 IU/kg every 14 days	0.0 (0.0 to 1.87) 1.08 (0.0 to 2.7)
Eftrenonacog alfa HB	BLONG (22) (<i>n</i> = 123)	50 IU/kg once per week 100 IU/kg every 10 days	3.0 (1.0 to 4.4) 1.4 (0.0 to 3.4)
Nonacog beta pegol HB	PARADIGM (23) (<i>n</i> = 59)	40 IU/kg once per week	1.0 (0.0 to 4.0)

HA, hemophilia A; HB, hemophilia B; IQR, interquartile range; IU, international units

Data concerning treatment is reported to the German Hemophilia Registry (DHR, Deutsches Hämophilie-register), which is run by the Paul Ehrlich Institute, in line with Section 21 of the German Transfusion Act (e3).

Methods

This review is based on a selective search of the literature in the MEDLINE/PubMed database using the relevant keywords (such as “new therapy options,” “randomized trial,” “hemophilia”) as well as expert opinions and recommendations of specialty societies. It examines both current treatment options and treatments currently being developed. However, the empirical relevance of some data is limited by the rarity of hemophilia and low study participant numbers.

Aims of hemophilia treatment

The essentials of hemophilia treatment are established by legal regulations, guidelines on blood component and plasma derivative therapy, and consensus recommendations of scientific societies. According to these, the primary aim of treatment is to prevent hemorrhages (6, 7). The German Medical Association (Bundesärztekammer) is expected to publish its new cross-discipline guideline on blood component and plasma derivative therapy in 2020. This will take into account the newly approved treatment options for hemophilia.

As a rule, treatment should be provided at a hemophilia center or in cooperation with one. There are guidelines issued by the Thrombosis and Hemostasis Research Society (GTH, Gesellschaft für Thrombose- und Hämostaseforschung) on the structure of hemophilia centers and requirements for the care of patients with rare congenital or acquired hemophilic coagulation disorders (8).

The importance of prophylactic factor replacement

Because FVIII and FIX have short half-lives, frequent intravenous injections at body-mass-dependent doses are required. The recommended dose for prophylaxis in hemophilia A is 25 to 40 international units (IU)/kg 3 times per week; for hemophilia B it is 2 to 3 × 25 to 40 IU/kg per week (7). Dosing must be individually tailored and may vary according to the patient’s hemorrhage type and frequency, joint status, activity level, and pharmacokinetic profile (9).

Randomized clinical trials confirm the superiority of prophylactic factor replacement over on-demand treatment in protecting against hemorrhage and maintaining joint health: 65 children with severe hemophilia A aged up to 30 months were enrolled and monitored regularly up to the age of 6 years (10). Those receiving on-demand treatment (*n* = 33) had a significantly higher frequency of hemorrhages per year than the group receiving prophylactic factor replacement (*n* = 32) (standard deviation [SD] 17.69 ± 9.25 versus 3.27 ± 6.24; *p* < 0.001) and significantly worse joint status as determined by MRI (odds ratio [OR] 6.1; 95% confidence interval [CI]: [1.5; 24.4]).

In another randomized trial dating from 2017, a total of 84 patients aged 12 to 50 years with severe and moderate hemophilia A were recruited between 2008 and 2013 and monitored for 3 years (11). Median factor use per kilogram body weight (BW) and year was higher in the prophylaxis group (*n* = 42) than in the group receiving on-demand treatment (4102 IU, quartile 1 [Q1]: 3904, quartile 3 [Q3]: 4312 versus 1700 IU, Q1: 1124, Q3: 2263). The mean annual rate of hemarthrosis was 1.9 (SD 4.1) in the prophylaxis group, versus 28.7 (SD 18.8) in the group

FIGURE

Schematic representation of the mechanism of action of the bispecific antibody emicizumab (26)

Emicizumab takes on the function of FVIII and binds to factor IXa with one arm and to its substrate, factor X, with the other arm. This initiates the FIXa-mediated activation of FX, forming the tenase complex. In this way, the coagulation cascade can be triggered even without FVIII. The active agent is not affected by FVIII inhibitors.

receiving on-demand treatment. Fifteen patients in the prophylaxis group had no hemorrhages at all during the trial period. Furthermore, the group receiving on-demand treatment made more use of the following health services (11):

- Contact with hemophilia center: 2.43 times higher
- Contact with primary care physician: 3.17 times higher
- Laboratory tests: 1.79 times higher
- Joint surgery: 23.8% versus 9.5% (prophylaxis group)

Early prophylactic factor replacement also had a positive effect on inhibitor development. The retrospective CANAL study included 316 children with severe hemophilia A, who were treated for the first time with a factor VIII drug. Eighty-two of the patients (26%) developed a factor VIII inhibitor (12), while the 196 children who received regular prophylactic factor VIII replacement had a significantly lower risk of inhibitors (OR 0.4 [0.2; 0.8]) (e4).

Studies on the long-term progression of hemophilia show that despite early initiation of regular prophylactic factor replacement and the associated burden on patients there remains a risk of spontaneous hemorrhage and the development of hemophilic arthropathy

cannot be completely prevented (13, 14). Prospective data on 4899 US patients with hemophilia has shown that, despite improved availability of modern treatment options, around one-third of patients (35.5% of 1548 patients) with severe hemophilia born between 1983 and 1992 had more than 5 hemarthroses in 6 months, with restricted mobility in the affected joint in 14.8% of cases and long-term impairment in 5.8% of cases (13). German data covering a 26-year time-span shows that despite early initiation of prophylactic therapy damage to joints can be detected after 10 years, with the ankles affected earliest (14).

Extended-half-life drugs

The half-life of factor VIII in the plasma is 10 to 12 hours. That of factor IX is 16 to 18 hours. Factor drugs with extended half-lives can reduce injection frequency or increase trough levels. Various techniques are used to delay clearance, such as fusion techniques or pegylation (covalent binding of polyethylene glycol [PEG] at particular points on the FVIII molecule) (e5). Fusion involves other, recombinant proteins such as the Fc domain of immunoglobulins or albumin, which have a substantially longer half-life in the blood and protect against early degradation (e6, e7).

TABLE 2

Trial schedule for HAVEN 1 to 4 on emicizumab

Trial		Haven 1 (27)	Haven 2 (28)	Haven 3 (29)	Haven 4 (30)
Trial design		Partly randomized		Partly randomized	
Patient population		Adults (≥12 years) with inhibitors (n = 113)	Children (<12 years) with inhibitors (n = 88)	Adults (≥12 years) without inhibitors (n = 152)	Adults (≥12 years) with or without inhibitors (n = 41)
Previous treatment		BPD on-demand or prophylactic treatment	BPD on-demand or prophylactic treatment	FVIII on-demand or prophylactic treatment	FVIII/BPD on-demand or prophylactic treatment
Mean annualized hemorrhage rate* ² [95% CI]	BPD/FVIII on-demand treatment	23.3 [12.33; 43.89]	19.9* ¹	38.2 [22.9; 63.8]	–
	BPD/FVIII prophylactic treatment in previous NIS* ¹	15.7* ¹ [11.1; 22.3]		4.8* [3.2; 7.1]	–
	Emicizumab prophylactic treatment	Weekly: 2.9 [1.69; 5.02]	Weekly: 0.3 [0.17; 0.50]	Weekly: 1.5 [0.9; 2.5]	Every 4 weeks: 2.4 [1.4; 4.3]
			Every 2 weeks: 0.2 [0.03; 1.72] Every 4 weeks: 2.2 [0.69; 6.81]	Every 2 weeks: 1.3 [0.8; 2.3]	
Relative decrease in AHR	Versus prior on-demand treatment	87%; (RR: 0.13; p < 0.0001)	99% 95% CI: [97.7; 99.4]	96% (RR: 0.04; p < 0.001)	–
	Versus prior prophylactic treatment* ¹	79%; (p < 0.001)		68% (RR: 0.32; p < 0.001)	–

AHR, annualized hemorrhage rate; BPD, bypass drug; CI, confidence interval; NIS, noninterventional study

*¹Only in patients from earlier noninterventional study (HAVEN 1: n = 24, HAVEN 2: n = 18, HAVEN 3: n = 48)

*²Hemorrhage rate calculated using a negative binominal regression model versus conventional mean weighting of AHR in line with length of trial participation

The half-life of FVIII is limited by binding to von Willebrand factor (e8). For the dosing frequency to be reduced from 3 times to twice per week while maintaining coagulation factor levels, the half-life needs to be at least 1.3 times that of a standard FVIII drug (15). Recent findings from phase 1 and 2 trials shows further prolongation of half-life for a factor VIII drug bound to domain 3 of von Willebrand factor. In the future this may make once-weekly injections possible (e9).

Extended half-life FIX drugs have half-lives between 2.4 and 4.8 times longer than standard FIX drugs, making it possible to provide effective prophylactic treatment every 1 to 2 weeks. The safety profile has been described as comparable to that of standard FIX drugs (16). The various extended half-life drugs and the findings of the main studies of the authorized doses are summarized in the *eTable* and *Table 1*.

Pegylated drugs are authorized only for patients over the age of 12 years. The recommended dose and frequency can be tailored to individual patients' response.

During treatment with long-acting concentrates, blood factor level measurements may be falsely high or low; this means that specific tests are required for some drugs (24). Recommendations of physicians' associations in the UK and Belgium highlight the significance of pharmacokinetic measurement, varying individual response, and laboratory test variability in

determining blood factor levels. For patients whose lifestyles involve low activity levels it may be possible to reduce treatment frequency still further. Patients with moderate hemophilia may also benefit from extended half-life drugs (25, e17). Prescription data and socioeconomic analyses have been published for Italy, Sweden, and the USA, and according to these the reduced frequency of administration means that treatment with long-acting drugs is no more expensive (e18–e20).

Non-coagulation factor-based treatment for hemophilia

New treatment approaches aim to treat hemophilia without replacing coagulation factors, for example using factor analogs or by suppressing natural coagulation cascade antagonists.

Emicizumab is a bispecific humanized monoclonal antibody. In Germany it was authorized on February 23, 2018 for prophylactic treatment in patients with hemophilia A and inhibitors, and on March 13, 2019 for patients with severe hemophilia A and no inhibitors, of any age, at a dose of 1.5 mg/kg BW once weekly, 3 mg/kg once every 2 weeks, or 6 mg/kg BW once every 4 weeks (with a loading dose of 3 mg/kg BW per week for 4 weeks in all cases) (*Figure*) (26). FVIII or bypass drug treatment is also required for hemorrhages that occur during this therapy.

TABLE 3

Trials of gene therapy for hemophilia A and hemophilia B

Trial/sponsor, no. of trial participants	Hemophilia type	Vector	Rise in coagulation factor level	Fall in median hemorrhage rate	End of factor replacement in patients receiving prior prophylactic treatment	Rise in ALT and prednisolone treatment
SJCRH/UCL (35, 36) n = 10	Hemophilia B	AAV2/8	Dose-dependent FIX increase: 1 to 6%	15.5 (IQR 10.3 to 19.3) to 1.5 (IQR 1.0 to 4.0) In high-dose group 6 out of 10: From 16.5 (IQR 12.5 to 27.0) to 1.0 (0.8 to 2.5)	4 in 7	Transient in 4 out of 6 at highest dose
Spark Therapeutics (38) n = 10	Hemophilia B	AAV-Spark100 (bioengineered)	FIX increase between 14 and 81%	11.1 (0 to 48) to 0.4 (0 to 4)	7 in 7	Transient in 2 out of 10
UniQure (39) n = 10	Hemophilia B	AAV5	Dose-dependent increase to >5%	In higher-dose cohort with spontaneous hemorrhages: 3.0 to 0.9	8 in 9	Transient in 3 out of 10
Biomarin (40) n = 9	Hemophilia A	AAV5	Dose-dependent FVIII increase to >50% in 6 out of 7 at highest dose	16 (IQR 1 to 24) to 1 (IQR 1 to 2)	8 in 8	Transient in 6 out of 7

ALT, alanine transaminase; AAV, adeno-associated virus; IQR, interquartile range; FIX, coagulation factor IX; FVIII, coagulation factor VIII

In 4 different phase 3 trials (HAVEN 1 to HAVEN 4) (27–30), patients of various ages with hemophilia A, with and without inhibitors, showed a significant decrease in hemorrhages compared to their previously administered standard treatment with factor concentrates, whether intraindividually or versus a control group that continued with prophylactic or on-demand factor concentrate treatment (*Table 2*). The primary outcome was annualized rate of hemorrhages treated with factor or bypass concentrates. Other hemorrhage categories were also recorded (e.g. all hemorrhages, treated spontaneous hemorrhages, treated hemarthroses) but are not shown here.

In the HAVEN trials overall, 63 to 87% of patients had no treated hemorrhages. This figure rose to 86 to 94% with longer treatment periods (73 to 96 weeks) (e21).

Common side effects are local reactions at the injection site (occurring in 22% of patients in the HAVEN 4 trial [30]). Antibodies to emicizumab were found in 3.5% of HAVEN trial participants (e22). Three of the 105 patients in the HAVEN 1 trial suffered thrombotic microangiopathies associated with the administration of activated prothrombin complex concentrate to treat breakthrough bleeding in patients with inhibitor hemophilia (27). Later in the trial, emicizumab and activated prothrombin complex concentrate combination therapy was halted and hemorrhages were treated with rFVIIa only. A median follow-up period of 82.4 weeks revealed no other side effects (e22).

For the indications severe hemophilia A and inhibitor hemophilia, Germany's Institute for Quality and Efficiency in Health Care (IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheits-

wesen) and Federal Joint Committee (G-BA, Gemeinsamer Bundesausschuss) have not attested any quantifiable additional benefit of emicizumab (e23–e25). The guidelines of the U.K.'s National Institute for Health and Care Excellence (NICE) endorse the option of emicizumab treatment for patients with hemophilia A and inhibitors (e26).

A particular point to note when dealing with patients taking emicizumab is that even subtherapeutic emicizumab levels restore normal activated partial thromboplastin time (aPTT). This means that normal aPTT during emicizumab treatment does not rule out increased risk of hemorrhage (31). This important information is also communicated via patient cards. Either chromogenic factor tests or global coagulation tests such as thrombin generation are used for monitoring (31).

In cases of inhibitor hemophilia, bypass drug (rFVIIa) treatment should be halted 24 hours before switching from factor drug prophylaxis. Combination therapy with activated prothrombin complex concentrate should be avoided. In patients with severe hemophilia A, administration of FVIII drugs can be continued up to 7 days after the first administration of emicizumab (e27).

Other drug treatments with longer half-lives that are still being trialed, such as inhibition of tissue factor pathway inhibitor (TFPI), e.g. using the monoclonal antibody concizumab, (32) and antithrombin (using small interfering RNA molecules) (33), are also administered subcutaneously and are suitable for both hemophilia A and hemophilia B patients, with or without inhibitors, and potentially also for other hemorrhagic diseases.

TABBLE 4

Properties of new hemophilia treatment options

	Replacement with factor drugs	Emicizumab	Gene therapy
Type of application	Intravenous	Subcutaneous	Intravenous
Frequency of application	Several times per week	Once a week Once every 2 weeks Once every 4 weeks	Single
Hemophilia type	Hemophilia A or B	Hemophilia A, regardless of inhibitor status	Hemophilia A or B
Prophylactic efficacy	Effective prophylaxis	Lower hemorrhage rate than standard treatment	Lower hemorrhage rate than standard treatment
Hemorrhage treatment	Additional factor concentrates	Additional factor or bypass concentrates (rFVIIa)	No hemorrhages expected if coagulation factor levels return to normal
Risk of inhibitors	Increased	No effect	Unclear
Monitoring	Coagulation factor level measured	Specific or global coagulation tests	Coagulation factor level measured

Gene therapy for hemophilia

Unlike the treatment options described so far, gene therapy for hemophilia offers the prospect of the longest-lasting possible increase in factor levels, rising to normal levels. This would be achieved after a single infusion of a recombinant, adeno-associated virus (AAV)-based vector containing the gene for the missing coagulation factor. The infusion, which takes approximately 60 minutes, can now be administered on an outpatient basis. AAVs are used as viral vectors in *in vivo* gene therapy because they are not associated with diseases, they show strong liver tropism according to serotype, and the viral genetic material is not integrated into the genome of the host cell (34).

Initial, groundbreaking findings on gene therapy for hemophilia B were published in 2011 and 2014 (35, 36). We can now look back over continuous gene expression for the last 8 years. In that time not even delayed side effects have been reported (37). *Table 3* summarizes the findings of the phase 1 trials on gene therapy for hemophilia A and B published to date. Various phase 3 trials in larger populations of adult patients with severe hemophilia and no inhibitors are currently ongoing.

Most studies exclude patients with neutralizing antibodies to AAV. These are found in up to 50% of the population (e28). Furthermore, potential immunological, transient liver toxicity (raised alanine transaminase [ALT] level) has been observed in some patients. In some cases this led to reduced efficacy (35–40).

Prospects

The new treatment options are based on new mechanisms of action, and some can be applied subcutaneously with longer half-lives. A further advantage is their broad spectrum of application, in some cases in patients with either hemophilia A or with hemophilia B

and inhibitors. *Table 4* summarizes the properties of the new hemophilia treatment options.

The availability of alternatives to conventional replacement therapy will require that pertinent treatment algorithms be developed. The extent to which new treatment forms will unsettle factor replacement as first-line treatment for hemophilia A, and immune tolerance therapy as first-line treatment for inhibitor hemophilia, is unclear. Evidence-based recommendations on first-line treatment and switching to new treatment options are still pending, as is long-term safety data, particularly for additional combination therapy with factor or bypass concentrates required for hemorrhages or surgeries.

There is no need for general monitoring of the response to subcutaneous therapy because its dosing is fixed; this is in any case impossible with conventional coagulation tests. Specific or global coagulation tests can be used to estimate the effect on coagulation. As the new treatments are complex and interact with coagulation factor drugs and laboratory tests, treatment should be provided at a hemophilia center with relevant experience. A systematic, quality-assured training program for physicians, patients, and parents is important regarding the new treatment options specifically.

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Conflict of interest statement

Prof. Miesbach has received consultancy fees from Bayer, BioMarin, Biotest, CSL Behring, Chugai, Freeline, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Takeda/Shire, and uniQure. He has received reimbursement of participation fees for conferences from Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, and Takeda/Shire. He has received fees for preparing scientific events from Bayer, Biotest, CSL Behring, Octapharma, Sobi, Novo Nordisk, Pfizer, Stago, and Takeda/Shire. Fees for research initiated by him have been paid into a third-party account by Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, Stago, Pfizer, Takeda/Shire, and Werfen.

Key messages

- Standard treatment for hemophilia consists of prophylactic administration of a coagulation factor concentrate. This must be performed several times a week (intravenously).
- Long-acting coagulation factor drugs can lengthen the time between treatments or increase coagulation factor levels.
- New treatment options are based on new mechanisms of action and can be administered subcutaneously, sometimes with an extended half-life and a broad spectrum of application for hemophilia A, hemophilia B, and inhibitor hemophilia.
- Emicizumab, which has already been authorized for use in Germany, significantly reduced hemorrhage rates in patients with hemophilia A, regardless of inhibitor status.
- Long-term safety data and data on concomitant use of factor or bypass concentrates are still pending.
- Clinical trials of gene therapy have been successful for both hemophilia A and hemophilia B. In some cases, normal coagulation factor levels have been achieved.

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CLINICAL SNAPSHOT

Sister Mary Joseph Nodule

A 44-year-old man presented with a painless umbilical nodule 2 cm in diameter (*Figure*). The nodule had first come to his attention 2 months previously and had been getting progressively larger. The patient reported that he had been suffering from primarily biliary cholangitis for 2 years. Histopathological examination of a biopsy sample showed adenocarcinoma. Subsequent investigations identified the presence of metastasized cholangiocellular carcinoma. Despite swift commencement of chemotherapy, the patient died of his disease. Sister Mary Joseph Dempsey (1856–1939), a nun working as a nurse, repeatedly observed the rare phenomenon of umbilical metastasis and reported it to her departmental head physician W.J. Mayo, one of the founders of the Mayo Clinics. He then published a description of the association in 1928. In most cases the umbilical cutaneous metastasis termed Sister Mary Joseph nodule arises from a gastrointestinal tumor, less frequently from a genitourethral tumor. The metastasization usually occurs via an interface of the deep and superficial lymph drainage pathways with the skin of the umbilicus.

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eTABLE

Increase in half-lives of FVIII and FIX drugs*

	Drug	Technology	Increase in $t_{1/2}$
Hemophilia A	Damoctocog alfa pegol (e10)	Pegylation (60 kDa)	1.42
Hemophilia A	Efmoroctocog alfa (e11)	Fusion with Fc fragment of IgG1	1.53
Hemophilia A	Rurioctocog alfa pegol (e12)	Pegylation (20 kDa PEG)	1.36
Hemophilia A	Turoctocog alfa pegol (e13)	Pegylation (40 kDa PEG)	1.62
Hemophilia B	Albutrepenonacog alfa (e14)	Fusion with recombinant albumin	2.4
Hemophilia B	Eftrenonacog alfa (e15)	Fusion with Fc fragment of IgG1	4.2
Hemophilia B	Nonacog beta pegol (e16)	Pegylation (40 kDa PEG)	4.8

*Increase in half-life compared to the same dose of a standard drug
 $t_{1/2}$, half-life; FVIII, factor VIII; FIX, factor IX