Treatment of Inherited Platelet Disorders: Current Status and Future Options

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Abstract

Inherited platelet disorders (IPDs) comprise a heterogeneous group of entities that manifest with variable bleeding tendencies. For successful treatment, the underlying platelet disorder, bleeding severity and location, age, and sex must be considered in the broader clinical context. Previous information from the AWMF S2K guideline #086–004 (www.awmf.org) is evaluated for validity and supplemented by information of new available and future treatment options and clinical scenarios that need specific measures. Special attention is given to the treatment of menorrhagia and risk management during pregnancy in women with IPDs. Established treatment options of IPDs include local hemostatic treatment, tranexamic acid, desmopressin, platelet concentrates, and recombinant activated factor VII. Hematopoietic stem cell therapy is a curative approach for selected patients. We also provide an outlook on promising new therapies. These include autologous hematopoietic stem cell gene therapy, artificial platelets and nanoparticles, and various other procoagulant treatments that are currently tested in clinical trials in the context of hemophilia.

Keywords

- blood platelet disorder
- therapy
- inherited platelet disorder

Zusammenfassung

Angeborene Störungen der Thrombozyten umfassen eine heterogene Gruppe von Erkrankungen, die mit variabler Blutungsneigung einhergehen. Für eine erfolgreiche Behandlung müssen die zugrundeliegende Thrombozytenstörung, Blutungsschwere und -lokalisation, Alter und Geschlecht im klinischen Kontext berücksichtigt werden. Zuvor veröffentlichte Informationen aus der AWMF S2K-Leitlinie #086–004 (www.awmf.org) werden auf ihre Gültigkeit hin überprüft und durch Informationen zu neu verfügbaren und zukünftigen Behandlungsmöglichkeiten, sowie klinischen Szenarien, die spezifische Maßnahmen erfordern, ergänzt. Besonderes berücksichtigt werden die Behandlung von Menorrhagien, sowie das Risikomanagement während der Schwangerschaft bei Frauen mit angeborenen Thrombozytenerkrankungen. Etablierte Behandlungsmöglichkeiten umfassen die lokale Blutstillung, sowie die Verabreichung von Tranexamsäure, Desmopressin, Thrombozytenkonzentraten und rekombinantem, aktivierten Faktor VII. Die hämatopoetische Stammzelltherapie ist ein kurativer Ansatz für ausgewählte PatientInnen. Weiters wird ein Ausblick auf vielversprechende neue Therapien gegeben. Dazu gehören die autologe hämatopoetische Stammzell-

Schlüsselwörter

- Angeborene Thrombozytenerkrankung
- Therapie

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Gentherapie, künstliche Blutplättchen und Nanopartikel, sowie verschiedene andere prokoagulatorische Behandlungen, die bereits in klinischen Studien zur Behandlung der Hämophilie getestet werden.

Introduction

Inherited platelet disorders (IPDs) comprise a heterogenous group of more than 60 rare bleeding disorders with abnormal platelet function and/or low platelet count. The true prevalence is unknown, but estimation is at least 2.7 cases per 100,000.[1,2]

IPDs are characterized by highly variable clinical presentation and prognosis. Clinical complications range from almost negligible to life-threatening. Some manifest as isolated platelet disorders, while others are associated with a variety of other abnormalities (syndromic), and still others predispose to the development of hematological malignancy and bone marrow aplasia.[2–5]

IPDs may remain unnoticed for many years with up to 60% of cases with proven platelet defects that cannot be assigned to any pre-described IPD.[6] Moreover, genotype–phenotype correlation of different types of mutations is mostly poorly defined.[7]

Typical clinical symptoms of IPDs are mucocutaneous bleeding including epistaxis, oral cavity bleeding, purpura, hematomas, and heavy menstrual bleeding (HMB). In case of trauma and surgical intervention, clinically relevant bleeding and blood loss may occur unexpected and independent of platelet count.[1–4]

Although many efforts have been made on diagnosing and characterizing IPDs and "new disorders" are identified on a regular and frequent basis, therapeutic options for the prevention and treatment of bleeding due to IPDs remain limited.

Since 2014, the THROMKIDplus working group of the "Gesellschaft für Thrombose- und Hämostaseforschung e. V." (GTH) aims to develop and distribute useful guidelines for the diagnosis as well as treatment of platelet disorders.[8] This article updates previous information and presents current knowledge on treatment options, which are supplemented by clinical scenarios that need specific measures. For treatment details including dosing, readers are referred to the AWMF guideline on treatment of platelet disorders (AWMF S2K guideline #086–004; www.awmf.org).[9]

Methods

A literature search strategy was developed by consulting the PubMed platform of the National Center for Biotechnology Information (NCBI). The literature search included peer-reviewed articles, published in English and German language, updated from January 2018 to January 2023. We used the MeSH term "blood platelet disorders" *and* the search terms "tranexamic acid" *or* "platelet concentrate" *or* "rFVIIa" *or* "eptacog alfa" *or* "eptacog beta" *or* "desmopressin" *or* "splenectomy" *or* "fitusiran" *or* "concizumab" *or* "marstacimab" *or* "befovacimab" *or* "haematopoietic stem cell transplantation" *or* "gene therapy". A total of 521 references were screened for their relevance and quality. Of these, 100 articles including review articles, guidelines, meta-analyses, and additional literature from the respective reference sections (►**Supplementary Fig. S1**, available in the online version only). For the outlook section (future therapies), we also searched clinicaltrials.gov using the term "blood platelet disorder." Additionally, results from personal communication within the THROMKIDplus working group during the pediatric GTH (pedGTH) meeting held in September 2022 in Igls (Austria) were included.

Current Treatment Options

General Considerations

Today any possible effort to achieve the classification of the underlying platelet defect, including molecular genetic testing, is imperative to guide clinical management. For adequate prevention and treatment of bleeding, a distinction between IPDs with mere platelet function defect and those with (additional) low platelet count is important (►**Table 1**).

Many commonly used drugs affect platelet function and should be avoided including frequently prescribed nonsteroidal anti-inflammatory drugs, particularly acetylsalicylic acid and selective serotonin reuptake inhibitors.[1–3,10] Selective COX-2 inhibitors without effect on platelet function may be used for pain control, but are approved for use only from the age of 16 years.[11]

Testing for iron-deficiency anemia in patients with frequent bleedings should be performed on a regular basis.[12] Adequate treatment is provided by oral and/or intravenous iron supplementation.[12]

A good dental hygiene is essential to prevent gum bleeding and tooth loss.[2,13] Recommended vaccinations should not be withheld but administered preferentially subcutaneously whenever approved.[14] As with other hemorrhagic disorders, children and families should be trained to avoid bleeding and carry an identification card with them bearing information about their medical condition.[3,15]

Local Hemostatic Treatment

Topical hemostatic measures are considered first-line treatment, irrespective of the underlying pathology. Mechanical hemostats include foams, sponges or gauze soaked with porcine gelatins, bovine collagen or oxidized regenerated cellulose, and polysaccharide spheres. Further biologically active hemostats with human, bovine, or recombinant thrombin are available. Fibrin sealants, tissue adhesives, and topical tranexamic acid (TXA) are successfully used in

Table 1 Overview of IPDs mentioned in this article

Disease	Gene	Underlying defect (size of thrombocytes: small [S], normal [N], large [L]), main features	Bleeding tendency
***Nonsyndromic** IPDs with **normal** platelet count and abnormal platelet function*			
Glanzmann thrombasthenia	*ITGA2B, ITGB3*	Platelet receptor defect (N), bleeding tendency	Variable, but likely severe
***Nonsyndromic** IPDs with **low** platelet count*			
Bernard-Soulier syndrome	*GP1BA, GP1BB, GP9*	Platelet receptor defect (L), bleeding tendency	Variable, but likely severe
Platelet-type von Willebrand disease	*GP1BA*	Platelet receptor defect (L), platelet count may decrease under stress conditions	Absent to mild
***Syndromic** IPDs with **normal** platelet count*			
Chediak-Higashi syndrome	*LYST*	δ-Granule secretion defect (N), immunodeficiency with predisposition to recurrent infections, risk of accelerated phase of hemophagocytic lymphohistiocytosis, oculocutaneous albinism	Mild to moderate
***Syndromic** IPDs with **low** platelet count*			
WAS	*WAS, WIPF1*	Cytoskeleton defect (S), immunodeficiency, eczema, lymphoproliferative and autoimmune disorders	Variable
X-linked thrombocytopenia	*WAS*	Cytoskeleton defect (S), mild form of WAS	Absent to moderate
CAMT	*MPL*	Defect of megakaryopoiesis (N), progression to aplastic anemia	Variable
MECOM-related thrombocytopenia	*MECOM*	Defect of megakaryopoiesis (N), radioulnar synostosis, potential renal or cardiac anomalies, risk of sensorineural hearing loss	Severe
Thrombocytopenia with absent radii	*RBM8A*	Defect of megakaryopoiesis (N), bilateral absence of radius w/o other skeletal abnormalities, potential kidney, cardiac or central nervous system anomalies	Severe
THPO-related thrombocytopenia	*THPO*	Defect of megakaryopoiesis (N), biallelic mutations resemble CAMT	Severe
*IPDs with **low** platelet count and **predisposition to malignancy***			
FPD with propensity to AML	*RUNX1*	Defect of megakaryopoiesis (N), high risk (ca. 40%) of developing acute myeloid leukemia or myelodysplastic syndrome	Absent to moderate
Thrombocytopenia type 2	*ANKRD26*	Defect of megakaryopoiesis (N), risk (ca. 10%) of developing myeloid neoplasms	Absent to mild
Thrombocytopenia type 5	*ETV6*	Defect of megakaryopoiesis (N), predisposition (ca. 30%) to acquired lymphoid, myeloid, and myeloproliferative syndromes	Absent to mild

Abbreviations: AML, acute myeloid leukemia; CAMT, congenital amegakaryocytic thrombocytopenia; FPD, familial platelet disorder; IPDs, inherited platelet disorders; WAS, Wiskott-Aldrich syndrome.

bleeding disorders.[3,16–18] Chitosan-covered gauze is an efficient local treatment option in postpartum hemorrhage and proved to support wound healing.[19,20]

Tranexamic Acid

TXA inhibits activation from plasminogen to plasmin and thus inhibits fibrinolysis and supports clot formation. TXA administered parenterally, locally, or as mouth wash is generally recommended in IPDs. Combination with other hemostatic treatment options including recombinant activated factor VII (rFVIIa), and desmopressin (DDAVP), and long-term therapy is recommended and reasonable in selected cases. Occasionally, headache or gastrointestinal side effects such as nausea, vomiting, and diarrhea may occur.[21] TXA is contraindicated in patients with a history of or in acute arterial or venous thrombosis, in severe renal

insufficiency, and should not be given to patients with bleeding in the urogenital region or the pleural space, because of increased risk of insoluble hematomas.[22] TXA can cause postoperative seizures, especially in cardiac surgery patients, and is therefore contraindicated in patients with a history of seizures.[23]

Desmopressin

DDAVP is a synthetic analog of the antidiuretic hormone L-arginine vasopressin, and has an antidiuretic but not a vasoconstrictive effect. DDAVP develops its hemostatic effect by increasing levels of von Willebrand factor (VWF), Factor VIII, and platelet adhesiveness, although its exact mechanisms remain unknown.[3,15,24–26] In patients with IPDs, DDAVP induces the formation of procoagulant platelets.[27] Repeated administration leads to prompt decrease in response of the hemostatic effect (tachyphylaxis).[3,15,24–26]

Since the 1980s, DDAVP has been successfully used for the treatment of mild to moderate hemophilia A and von Willebrand disease type 1. Subsequently, the spectrum of clinical applications has been expanded to platelet disorders, especially storage pool diseases, where efficacy was demonstrated in some, but not all, cases.[3] DDAVP is usually considered ineffective in patients with Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS).[3,28,29] There is only poor evidence to support testing DDAVP responsiveness in patients with IPDs.[16,29]

Due to its effect on fluid retention and consecutive hyponatremic seizures, monitoring of vital functions and sodium plasma levels is indicated and fluid intake should be restricted. According to the AWMF guidelines on the treatment of IPDs (AWMF S2K guideline #086–004; www.awmf.org), DDAVP is not recommended in children younger than 3 years or in children with seizures in their history. The same applies for pregnant women and many other patients with cardiac and vascular conditions.[3,15,16,25,29]

Transfusion of Platelet Concentrates

Platelet concentrates (PCs) are commonly administered to prevent and treat bleeding in IPDs with severe bleeding phenotype. At least in acquired thrombocytopenia, recent data have highlighted uncertainties in the risk–benefit ratio (►Fig. 1).[30] In neonates, it has been shown that liberal transfusion of PCs increases the risk of hemorrhage and mortality.[31,32] Using PCs bears an inherent risk of alloimmunization, transfusion-transmitted infections, and allergic reactions.[1,3,15,16,25,33] PCs can be obtained either from apheresis (single donor) or from pools of buffy-coats (four to six donors).[33] In IPDs, PCs from a single-donor, leukocyte depleted, and, if available, human leukocyte antigen (HLA)-matched are preferred due to a lower risk of immunization.[1,3] After administration of PCs, the platelet count should always be reevaluated.

In GT and BSS patients, platelets are deficient in specific glycoproteins (GPs), so patients are at risk to develop antibodies against GPs (in GT: anti-GP IIb/IIIa, in BSS: anti-GP1b/IX) and become refractory to PCs.[3,34] In GT patients, a past history of immunization, GT type 1, and female sex might increase the risk of immunization against GPIIb/IIIa and favor therapy with rFVIIa over PCs.[35] In the presence of platelet antibodies, an increased dose of PCs in combination with rFVIIa or VWF may control bleeding.[25] In case of high

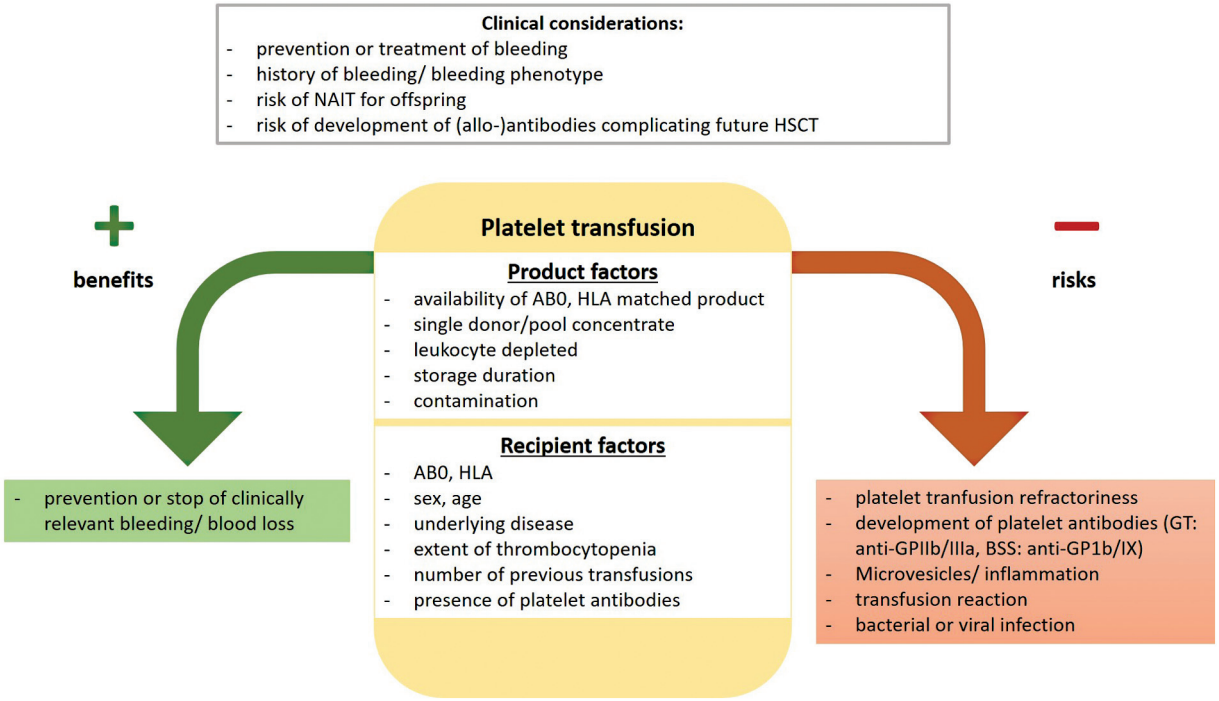

Fig. 1 Benefits and risks of platelet transfusions depending on platelet product and recipient. BSS, Bernard-Soulier syndrome; GT, Glanzmann thrombasthenia; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; NAIT, neonatal alloimmune thrombocytopenia.

Table 2 Future directions of management of inherited platelet disorders

What we have to do in the future
Decrease the rate of unidentified but suspected platelet defects • 60% of suspected cases remain poorly described/classified
Introduce general use of bleeding scores to assess individual bleeding tendency
Develop escalating treatment strategies for prevention *and* treatment of bleeding episodes
Include patients with IPDs and bleeding in clinical trial programs
Establish registries to elucidate the clinical course of IPDs
Develop and adapt laboratory tests to monitor treatment success beyond clinical assessment
Identify and publish centers with expertise in advanced platelet diagnostics and IPD genetic testing
Ameliorate training of pediatric hematology/oncology treatment centers to increase awareness of IPDs versus other entities, especially those with low platelet count including chronic ITP

Abbreviations: IPDs, inherited platelet disorders; ITP, immune thrombocytopenia.

urgency, immunoadsorption is another method to reduce antiplatelet antibodies.[35–37] Flow cytometric analysis of GPIIb (IIb integrin)/GPIIIa (CD41/CD61) and GPIbα (CD42b), respectively, is recommended for monitoring the presence of transfused platelets.[8] Three months after receiving a PC, testing for platelet-specific antibodies is highly recommended.[16,25]

Recombinant Activated FVII (Eptacog Alfa and Eptacog Beta)

Eptacog alfa develops its procoagulant activity through a tissue factor dependent and independent thrombin burst.[15] It is approved for GT with or without antibodies to GP IIb/IIIa (integrin) and with past or present refractoriness to platelet transfusions. In 2018, the European Medicines Agency (EMA) extended the approval for those patients when platelets are not readily available.[25,38] Its off-label use has shown benefits in patients with BSS,[39,40] storage pool diseases,[40] platelet type von Willebrand disease,[41] and thrombocytopenia with absent radii (TAR) syndrome.[42]

Eptacog beta has been approved for the treatment of hemophilia A and B with inhibitors in July 2022 in Europe. So far, no reports on its use in IPDs have been published.

In case of acute bleeding in patients with IPDs, of the aforementioned treatment options, local measures and TXA are the first choice. If bleeding cannot be adequately controlled, PCs and rFVIIa are options for further therapy escalation. PCs should be administered restrictively in patients with GT and BSS due to the risk of platelet antibody formation. DDAVP should not be administered in case of severe bleeding and should be administered only after a trial.

Thrombopoietin Receptor Agonists

The two thrombopoietin receptor agonists, eltrombopag and romiplostim, are currently approved for immune thrombocytopenia (ITP), thrombocytopenia in adult patients with hepatitis C infection, and severe aplastic anemia in adults.[43] Both drugs have shown effects in IPDs. For further details, readers are referred to the article Thrombopoietin receptor agonists for treatment of thrombocytopenias in pediatrics in the next issue of the journal.

Splenectomy

Splenectomy is generally not recommended.

In Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia, microplatelets and thrombocytopenia are caused by sequestration in the spleen.[7,45,46] After splenectomy, platelet size and count normalize, leading to a significant reduction of bleeding episodes.[46] Also in WAS, splenectomy should be performed very cautiously to avoid aggravation of infectious risk and impaired recovery following allogeneic hematopoietic stem cell transplantation (HSCT).[47]

Allogeneic Hematopoietic Stem Cell Transplantation

HSCT is a curative treatment option for some IPDs but due to associated risks, including development of graft-versus-host disease (GvHD), graft rejection, infections, and toxicities, it is reserved for selected patients.[48]

HSCT should be considered in the presence of severe bleeding tendency, as in GT[49–53] and BSS[54] with refractoriness to platelet transfusion.

Furthermore, HSCT should be considered in syndromic IPDs, in which bleeding tendency is mild to moderate and other symptoms predominate.

In WAS, immunodeficiency and often severe symptoms of autoimmune response call for early HSCT. In fact, HSCT should already be considered at the time of diagnosis, as it should ideally be performed in children younger than 2 years, before disease progresses.[3,55,56]

Patients with Chediak-Higashi syndrome, particularly those with lacking cytotoxic T-lymphocyte function, are at risk of developing hemophagocytic lymphohistiocytosis. In such cases, early HSCT should be considered.[57–60]

Patients with congenital amegakaryocytic thrombocytopenia usually develop bone marrow failure within the first decade of life. They can be cured by HSCT. In contrast, a subgroup of patients with mutations in the gene encoding thrombopoietin does not benefit from HSCT.[45,61–64]

MDS1 and EVI1 complex locus–associated syndrome manifests as congenital radioulnar synostosis and amegakaryocytic thrombocytopenia progressing to pancytopenia and can be cured by HSCT.[65,66]

HSCT should also be considered for IPDs with a known risk for development of malignancy. Among those are germline autosomal dominant mutations in RUNX1 (familial platelet disorder with propensity to acute myeloid leukemia), ANKRD26 (thrombocytopenia type 2), and ETV6 (thrombocytopenia type 5).[67] As bleeding tendency is mild, and platelet number is only slightly reduced, these entities may be overlooked or even misdiagnosed as ITP. Once malignancy develops, HSCT may become necessary.[1,68–71]

Gene Therapy

Gene therapy is based on transfer of genetic material into the cells of patients, and various types of gene therapy have led to therapeutic breakthroughs in different diseases.[72] It is a potential alternative to HSCT for patients with WAS lacking a suitable donor. Furthermore, gene therapy requires a less toxic conditioning scheme and the risk of GvHD, and rejection is reduced compared with HSCT.[7,72] So far, across the spectrum of IPDs, the only approach that has reached clinical stages of development is autologous hematopoietic stem cell gene therapy in WAS.[73–77]

In a phase I/II pilot trial in 10 patients with WAS, a gamma-retroviral vector was used.[73] Results showed a good response in terms of reduction of infections and of clinical signs of autoimmunity (autoimmune cytopenia, colitis, eczema), and elevation of platelet count in nine out of ten patients. However, vector-mediated insertional mutagenesis led to the development of acute leukemia in seven out of ten patients.[73] As a consequence, subsequent trials used a self-inactivating lentiviral vector. A long-term follow-up over 4 to 9 (median: 7.6) years after gene therapy within an open-label, phase I/II clinical trial found resolution of severe infections and eczema, improvement of autoimmune disorders, and bleeding frequency.[75] Notably, there was no occurrence of malignancy. Even though platelet number was under normal threshold levels and platelet size was still smaller and showed decreased α-granule density in six out of nine patients after gene therapy, none of the patients needed PCs. Despite incomplete correction of the platelet compartment, no spontaneous bleeding occurred.[74–77]

Up to now, only one patient has undergone successful gene therapy in an adult age, for whom no donor for HSCT could be found.[78]

There are promising preclinical studies and animal models for gene therapy in GT. Fang et al showed in a murine and a canine model that infusion of ex vivo lentiviral transduced hematopoietic stem cells resulted in circulating platelets with approximately 10% of normal integrin (αIIbβ3) levels, which was enough for the improvement of hemostasis.[75,79,80]

Special Recommendations for Women with IPDs

Heavy Menstrual Bleeding

HMB is a common complaint in female adolescents. In 10 to 62%, there exists an underlying bleeding disorder, in up to 44% of IPD.[81,82] TXA is considered the first choice of treatment in women with HMB, in the case of acute intervention, as well as long-term treatment in women who seek to conceive.[11,83] If TXA alone is insufficient, a combination with DDAVP may be considered, but it is not recommended in the case of major blood loss.[11] In patients who do not want to conceive, menorrhagia should be controlled by hormones. Among all options, a levonorgestrel-releasing intrauterine device (LNG-IUD) is the most effective therapy.[11,84] If LNG-IUD is contraindicated or objected by the patient, combined oral contraceptives (COC) are suggested. If hormonal treatment fails or is insufficient, combination with TXA is recommended and is particularly effective in patients with GT and BSS.[11,83] Surgical options like endometrial ablation or hysterectomy should be considered only if the earlier-mentioned medical therapies fail and there is no desire to conceive in the future (see ►Fig. 2).[11,83]

Risk Management in Pregnancy

Women with IPDs with previous menorrhagia, who stop taking COC to conceive, are at high risk of developing HMB in the prepregnancy period.[85] Treatment options include TXA and rFVIIa.[85] Particularly in women with GT, but also with BSS, PCs should be avoided in order not to increase the risk of platelet antibody formation.[85,86] Platelet antibodies can cross the placenta, causing fetal or neonatal harm.[85–87] Neonatal alloimmune thrombocytopenia may occur in up to 30% of newborns of mothers with GT.[88] Thus, before and during pregnancy, antibodies should be monitored. In case of high levels, intravenous immunoglobulins and/or corticosteroids should be considered during pregnancy.[85,86]

Potential Future Treatments of IPDs

Artificial Platelets

In a first-in-human trial, pluripotent stem cells were generated from a patient's peripheral blood and differentiated into immortalized megakaryocyte progenitor cell lines. A clone of those was then induced to produce pluripotent stem cell–derived platelets (iPSC-PLTs), which were successfully transfused for treating severe aplastic anemia in a 55-year-old woman without complications when followed up for 1 year.[89] This trial of iPSC-PLTs administration not only showed promising results but raised expectations to generate HLA-class-I–depleted platelets or gene-corrected platelets as well.[89–91]

Platelet-Inspired Nanoparticles

The surfaces of nanoparticles and microparticles (liposomes, latex beads, and albumin-based microparticles) are modified with platelet surface-relevant ligands and GPs to support various platelet mechanisms. For example, micro- or nanoparticles are coated with fibrinogen, GPIbα and recombinant GPIa/IIa, collagen-binding peptide, and von Willebrand binding peptide. Results from in vitro and animal models are encouraging.[19,92–95]

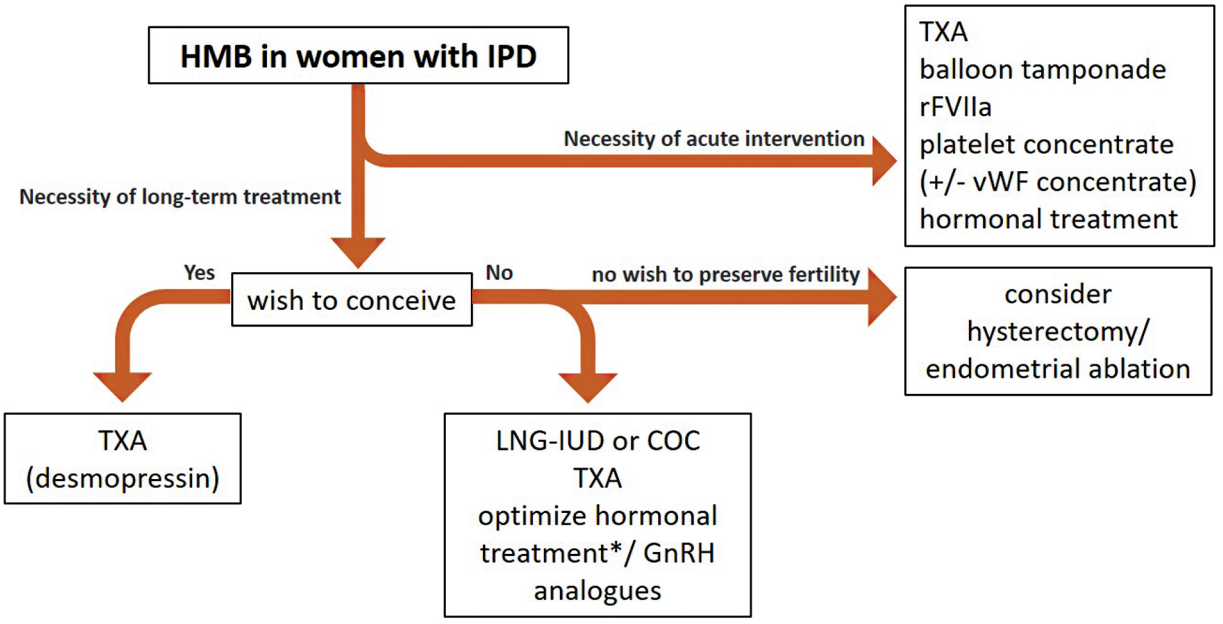

Fig. 2 Therapeutic algorithm of heavy menstrual bleeding in women with inherited platelet disorders. *Progestogens: systemic high dose, continuous or cyclical progestogen, depot, or implant. COC, combined oral contraceptives; HMB, heavy menstrual bleeding; IPD, inherited platelet disorder; LNG-IUD, levonorgestrel-releasing intrauterine device; rFVIIa, recombinant activated factor VII; TXA, tranexamic acid; vWF, von Willebrand factor.

HMB-001

HMB-001 is a bispecific antibody that binds endogenous FVIIa and platelet triggering receptor expressed on myeloid cells (TREM)-like transcript-1 receptor, which is present on the surface of activated platelets. Thereby HMB-001 promotes local FX activation and thrombin generation and thus restores clot formation in patients with GT and BSS.[96]

Various Other Therapies to Achieve Hemostatic Correction

Tissue factor pathway inhibitors (TFPIs) influence the early stages of blood coagulation. Anti-TFPIs include concizumab, marstacimab, and befovacimab and have been evaluated for use in patients with hemophilia.[97–99] Fitusiran is a small interfering RNA therapy that reduces antithrombin production, resulting in less bleeding episodes in hemophiliacs.[100] In contrast to activated factor VII, which leads to an instant thrombin burst, all these new drugs develop their effect on coagulation continuously. Severe bleeding in IPDs occurs frequently in women taking hormones. All of these may increase the risk of thromboembolic events during long-term prophylaxis. So far, TFPIs and fitusiran are still in clinical development stages and there are no reports on their use in IPDs.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

1 Palma-Barqueros V, Revilla N, Sánchez A, et al. Inherited platelet disorders: an updated overview. Int J Mol Sci 2021;22(09):4521
2 Balduini CL, Pecci A, Noris P. Inherited thrombocytopenias: the evolving spectrum. Hamostaseologie 2012;32(04):259–270
3 Bolton-Maggs PHB, Chalmers EA, Collins PW, et al; UKHCDO. A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Br J Haematol 2006;135 (05):603–633
4 Noris P, Pecci A. Hereditary thrombocytopenias: a growing list of disorders. Hematology (Am Soc Hematol Educ Program) 2017; 2017(01):385–399
5 Haley KM. Platelet disorders. Pediatr Rev 2020;41(05):224–235
6 Greinacher A, Eekels JJM. Simplifying the diagnosis of inherited platelet disorders? The new tools do not make it any easier. Blood 2019;133(23):2478–2483
7 Balduini CL. Treatment of inherited thrombocytopenias [in German]. Haematologica 2022;107(06):1278–1292
8 Streif W, Knöfler R, Eberl W, et al. Therapie hereditärer thrombozytopathien. Hamostaseologie 2014;34(04):269–275
9 S2K Leitlinie #086-004, Therapie angeborener thrombozytärer Erkrankungen. Version 2.1. Stand 02.04.2020. AWMF online: https://register.awmf.org/de/leitlinien/detail/086-004. Accessed June 10, 2023
10 Halperin D, Reber G. Influence of antidepressants on hemostasis. Dialogues Clin Neurosci 2007;9(01):47–59
11 Curry N, Bowles L, Clark TJ, et al. Gynaecological management of women with inherited bleeding disorders. A UK Haemophilia Centres Doctors' Organisation Guideline. Haemophilia 2022;28 (06):917–937
12 Lee A, Maier CL, Batsuli G. Iron deficiency anemia and bleeding management in pediatric patients with Bernard-Soulier syndrome and Glanzmann Thrombasthenia: a single-institution analysis. Haemophilia 2022;28(04):633–641
13 Salem K, Eshghi P. Dental health and oral health-related quality of life in children with congenital bleeding disorders. Haemophilia 2013;19(01):65–70

14 Makris M, Conlon CP, Watson HG. Immunization of patients with bleeding disorders. Haemophilia 2003;9(05):541–546
15 Alamelu J, Liesner R. Modern management of severe platelet function disorders. Br J Haematol 2010;149(06):813–823
16 Lee A, Poon MC. Inherited platelet functional disorders: general principles and practical aspects of management. Transfus Apheresis Sci 2018;57(04):494–501
17 Gabay M, Boucher BA. An essential primer for understanding the role of topical hemostats, surgical sealants, and adhesives for maintaining hemostasis. Pharmacotherapy 2013;33(09): 935–955
18 Ak G, Alpkılıç Başkırt E, Kürklü E, Koray M, Tanyeri H, Zülfikar B. The evaluation of fibrin sealants and tissue adhesives in oral surgery among patients with bleeding disorders. Turk J Haematol 2012;29(01):40–47
19 Dong R, Zhang H, Guo B. Emerging hemostatic materials for non-compressible hemorrhage control. Natl Sci Rev 2022;9(11): nwac162
20 Dueckelmann AM, Hinkson L, Nonnenmacher A, et al. Uterine packing with chitosan-covered gauze compared to balloon tamponade for managing postpartum hemorrhage. Eur J Obstet Gynecol Reprod Biol 2019;240:151–155
21 McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs 2012;72(05):585–617
22 Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al; Treatment Guidelines Working Group on Behalf of the World Federation of Hemophilia. Guidelines for the management of hemophilia. Haemophilia 2013;19(01):e1–e47
23 Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: causes and treatment. Ann Neurol 2016;79(01):18–26
24 Nurden AT, Freson K, Seligsohn U. Inherited platelet disorders. Haemophilia 2012;18(Suppl 4):154–160
25 Grainger JD, Thachil J, Will AM. How we treat the platelet glycoprotein defects; Glanzmann thrombasthenia and Bernard Soulier syndrome in children and adults. Br J Haematol 2018;182 (05):621–632
26 Tauer JT, Gneuss A, Lohse JE, Jürgens T, Knöfler R. Evaluation of desmopressin effect on primary haemostasis in pediatric patients with aspirin-like defect as hereditary thrombocytopathy. Klin Padiatr 2011;223(03):169–172
27 Colucci G, Stutz M, Rochat S, et al. The effect of desmopressin on platelet function: a selective enhancement of procoagulant COAT platelets in patients with primary platelet function defects. Blood 2014;123(12):1905–1916
28 Lozano M, Escolar G, Bellucci S, et al.1-Deamino (8-D-arginine) vasopressin infusion partially corrects platelet deposition on subendothelium in Bernard Soulier syndrome: the role of factor VIII, Platelets1999;10(02):141–145
29 Coppola A, Di Minno G. Desmopressin in inherited disorders of platelet function. Haemophilia 2008;14(Suppl 1):31–39
30 Stanworth SJ, Shah A. How I use platelet transfusions. Blood 2022;140(18):1925–1936
31 Ferrer-Marín F, Sola-Visner M. Neonatal platelet physiology and implications for transfusion. Platelets 2022;33(01):14–22
32 Fustolo-Gunnink SF, Roehr CC, Lieberman L, et al. Platelet and red cell transfusions for neonates: lifesavers or Trojan horses? Expert Rev Hematol 2019;12(10):797–800
33 Dupuis A, Gachet C. Inherited platelet disorders: management of the bleeding risk. Transfus Clin Biol 2018;25(03):228–235
34 Nurden P, Nurden AT. Congenital disorders associated with platelet dysfunctions. Thromb Haemost 2008;99(02): 253–263
35 Fiore M, d'Oiron R, Pillois X, Alessi MC. Anti-$\alpha_{IIb}\beta_3$ immunization in Glanzmann thrombasthenia: review of literature and treatment recommendations. Br J Haematol 2018;181(02):173–182
36 Ito K, Yoshida H, Hatoyama H, et al. Antibody removal therapy used successfully at delivery of a pregnant patient with Glanzmann's thrombasthenia and multiple anti-platelet antibodies. Vox Sang 1991;61(01):40–46
37 Martin I, Kriaa F, Proulle V, et al. Protein A Sepharose immunoadsorption can restore the efficacy of platelet concentrates in patients with Glanzmann's thrombasthenia and anti-glycoprotein IIb-IIIa antibodies. Br J Haematol 2002;119(04):991–997
38 Poon MC. The use of recombinant activated factor VII in patients with Glanzmann's thrombasthenia. Thromb Haemost 2021;121 (03):332–340
39 Ozelo MC, Svirin P, Larina L. Use of recombinant factor VIIa in the management of severe bleeding episodes in patients with Bernard-Soulier syndrome. Ann Hematol 2005;84(12):816–822
40 Almeida AM, Khair K, Hann I, Liesner R. The use of recombinant factor VIIa in children with inherited platelet function disorders. Br J Haematol 2003;121(03):477–481
41 Sánchez-Luceros A, Woods AI, Bermejo E, et al. PT-VWD posing diagnostic and therapeutic challenges - small case series. Platelets 2017;28(05):484–490
42 Coppola A, Simone CD, Palmieri NMA, et al. Recombinant activated factor VII for hemostatic cover of orthopedic interventions in a girl with thrombocytopenia with absent radii syndrome. Blood Coagul Fibrinolysis 2007;18(02):199–201
43 Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. Haematologica 2019;104(06):1112–1123
44 Meyer O, Dame C. Thrombopoietin receptor agonists for treatment of inherited thrombocytopenias in children and adolescents. Hamostaseologie 2023
45 Pecci A, Balduini CL. Inherited thrombocytopenias: an updated guide for clinicians. Blood Rev 2021;48:100784
46 Mullen CA, Anderson KD, Blaese RM. Splenectomy and/or bone marrow transplantation in the management of the Wiskott-Aldrich syndrome: long-term follow-up of 62 cases. Blood 1993;82(10):2961–2966
47 Ozsahin H, Cavazzana-Calvo M, Notarangelo LD, et al. Long-term outcome following hematopoietic stem-cell transplantation in Wiskott-Aldrich syndrome: collaborative study of the European Society for Immunodeficiencies and European Group for Blood and Marrow Transplantation. Blood 2008;111(01):439–445
48 Nathan S, Ustun C. Complications of stem cell transplantation that affect infections in stem cell transplant recipients, with analogies to patients with hematologic malignancies. Infect Dis Clin North Am 2019;33(02):331–359
49 Mathews N, Rivard GE, Bonnefoy A. Glanzmann thrombasthenia: perspectives from clinical practice on accurate diagnosis and optimal treatment strategies. J Blood Med 2021;12:449–463
50 Friend BD, Roach GD, Kempert PH, Moore TB. Successful use of hematopoietic stem cell transplantation for 2 pediatric cases of Glanzmann thrombasthenia and review of the literature. J Pediatr Hematol Oncol 2020;42(06):e521–e526
51 Flood VH, Johnson FL, Boshkov LK, et al. Sustained engraftment post bone marrow transplant despite anti-platelet antibodies in Glanzmann thrombasthenia. Pediatr Blood Cancer 2005;45(07): 971–975
52 Bellucci S, Devergie A, Gluckman E, et al. Complete correction of Glanzmann's thrombasthenia by allogeneic bone-marrow transplantation. Br J Haematol 1985;59(04):635–641
53 Bellucci S, Damaj G, Boval B, et al. Bone marrow transplantation in severe Glanzmann's thrombasthenia with antiplatelet alloimmunization. Bone Marrow Transplant 2000;25(03):327–330
54 Locatelli F, Rossi G, Balduini C. Hematopoietic stem-cell transplantation for the Bernard-Soulier syndrome. Ann Intern Med 2003;138(01):79
55 Rivers E, Worth A, Thrasher AJ, Burns SO. How I manage patients with Wiskott Aldrich syndrome. Br J Haematol 2019;185(04): 647–655
56 Imai K, Morio T, Zhu Y, et al. Clinical course of patients with WASP gene mutations. Blood 2004;103(02):456–464

57 Pettit RE, Berdal KG. Chédiak-Higashi syndrome. Neurologic appearance. Arch Neurol 1984;41(09):1001–1002
58 Umeda K, Adachi S, Horikoshi Y, et al. Allogeneic hematopoietic stem cell transplantation for Chediak-Higashi syndrome. Pediatr Transplant 2016;20(02):271–275
59 Lozano ML, Rivera J, Sánchez-Guiu I, Vicente V. Towards the targeted management of Chediak-Higashi syndrome. Orphanet J Rare Dis 2014;9(01):132
60 Eapen M, DeLaat CA, Baker KS, et al. Hematopoietic cell transplantation for Chediak-Higashi syndrome. Bone Marrow Transplant 2007;39(07):411–415
61 Woods G, Bajwa RPS, Rose MJ. Reduced intensity transplantation for congenital amegakaryocytic thrombocytopenia: report of a case and review of the literature. Pediatr Transplant 2014;18 (01):E31–E34
62 Ballmaier M, Germeshausen M. Congenital amegakaryocytic thrombocytopenia: clinical presentation, diagnosis, and treatment. Semin Thromb Hemost 2011;37(06):673–681
63 Capaci V, Adam E, Bar-Joseph I, Faleschini M, Pecci A, Savoia A. Defective binding of ETS1 and STAT4 due to a mutation in the promoter region of THPO as a novel mechanism of congenital amegakaryocytic thrombocytopenia. Haematologica 2022. Doi: 10.3324/haematol.2022.281392
64 Seo A, Ben-Harosh M, Sirin M, et al. Bone marrow failure unresponsive to bone marrow transplant is caused by mutations in *thrombopoietin*. Blood 2017;130(07):875–880
65 Germeshausen M, Ancliff P, Estrada J, et al. MECOM-associated syndrome: a heterogeneous inherited bone marrow failure syndrome with amegakaryocytic thrombocytopenia. Blood Adv 2018;2(06):586–596
66 Irie M, Niihori T, Nakano T, et al. Reduced-intensity conditioning is effective for allogeneic hematopoietic stem cell transplantation in infants with MECOM-associated syndrome. Int J Hematol 2023;117(04):598–606
67 Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391–2405
68 Feurstein S, Drazer MW, Godley LA. Genetic predisposition to leukemia and other hematologic malignancies. Semin Oncol 2016;43(05):598–608
69 Godley LA. Inherited predisposition to acute myeloid leukemia. Semin Hematol 2014;51(04):306–321
70 Galera P, Dulau-Florea A, Calvo KR. Inherited thrombocytopenia and platelet disorders with germline predisposition to myeloid neoplasia. Int J Lab Hematol 2019;41(Suppl 1):131–141
71 Churpek JE, Lorenz R, Nedumgottil S, et al. Proposal for the clinical detection and management of patients and their family members with familial myelodysplastic syndrome/acute leukemia predisposition syndromes. Leuk Lymphoma 2013;54(01): 28–35
72 Tang R, Xu Z. Gene therapy: a double-edged sword with great powers. Mol Cell Biochem 2020;474(1-2):73–81
73 Braun CJ, Boztug K, Paruzynski A, et al. Gene therapy for Wiskott-Aldrich syndrome - long-term efficacy and genotoxicity. Sci Transl Med 2014;6(254):1–15
74 Aiuti A, Biasco L, Scaramuzza S, et al. Lentiviral hematopoietic stem cell gene therapy in patients with Wiskott-Aldrich syndrome. Science 2013;341(6148):1233151
75 Magnani A, Semeraro M, Adam F, et al. Long-term safety and efficacy of lentiviral hematopoietic stem/progenitor cell gene therapy for Wiskott-Aldrich syndrome. Nat Med 2022;28(01): 71–80
76 Arruda VR, Weber J, Samelson-Jones BJ. Gene therapy for inherited bleeding disorders. Semin Thromb Hemost 2021;47(02):161–173
77 Ferrua F, Cicalese MP, Galimberti S, et al. Lentiviral haemopoietic stem/progenitor cell gene therapy for treatment of Wiskott-Aldrich syndrome: interim results of a non-randomised, open-label, phase 1/2 clinical study. Lancet Haematol 2019;6(05): e239–e253
78 Morris EC, Fox T, Chakraverty R, et al. Gene therapy for Wiskott-Aldrich syndrome in a severely affected adult. Blood 2017;130 (11):1327–1335
79 Fang J, Hodivala-Dilke K, Johnson BD, et al. Therapeutic expression of the platelet-specific integrin, alphaIIbbeta3, in a murine model for Glanzmann thrombasthenia. Blood 2005;106(08): 2671–2679
80 Fang J, Jensen ES, Boudreaux MK, et al. Platelet gene therapy improves hemostatic function for integrin alphaIIbbeta3-deficient dogs. Proc Natl Acad Sci U S A 2011;108(23): 9583–9588
81 Philipp CS, Faiz A, Dowling N, et al. Age and the prevalence of bleeding disorders in women with menorrhagia. Obstet Gynecol 2005;105(01):61–66
82 O'Brien B, Mason J, Kimble R. Bleeding disorders in adolescents with heavy menstrual bleeding: the Queensland Statewide Paediatric and Adolescent Gynaecology Service. J Pediatr Adolesc Gynecol 2019;32(02):122–127
83 Zia A, Kouides P, Khodyakov D, et al. Standardizing care to manage bleeding disorders in adolescents with heavy menses - a joint project from the ISTH pediatric/neonatal and women's health SSCs. J Thromb Haemost 2020;18(10):2759–2774
84 Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels JECLIPSE Trial Collaborative Group. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. N Engl J Med 2013;368 (02):128–137
85 Fiore M, Sentilhes L, d'Oiron R. How I manage pregnancy in women with Glanzmann thrombasthenia. Blood 2022;139(17): 2632–2641
86 Peitsidis P, Datta T, Pafilis I, Otomewo O, Tuddenham EGD, Kadir RA. Bernard Soulier syndrome in pregnancy: a systematic review. Haemophilia 2010;16(04):584–591
87 Siddiq S, Clark A, Mumford A. A systematic review of the management and outcomes of pregnancy in Glanzmann thrombasthenia. Haemophilia 2011;17(05):e858–e869
88 Barg AA, Hauschner H, Luboshitz J, et al. From thrombasthenia to next generation thrombocytopenia: neonatal alloimmune thrombocytopenia induced by maternal Glanzmann thrombasthenia. Pediatr Blood Cancer 2018;65(12):e27376
89 Sugimoto N, Kanda J, Nakamura S, et al. iPLAT1: the first-in-human clinical trial of iPSC-derived platelets as a phase 1 autologous transfusion study. Blood 2022;140(22):2398–2402
90 Xia L. Engineered platelets for clinical application: a step closer. Blood 2022;140(22):2314–2315
90 Xia L. Engineered platelets for clinical application: a step closer. Blood 2022;140(22):2314–2315
92 Farokhzad OC. Nanotechnology: platelet mimicry. Nature 2015; 526(7571):47–48
93 Girish A, Jolly K, Alsaadi N, et al. Platelet-inspired intravenous nanomedicine for injury-targeted direct delivery of thrombin to augment hemostasis in coagulopathies. ACS Nano 2022;16(10): 16292–16313
94 Raghunathan S, Rayes J, Sen Gupta A. Platelet-inspired nanomedicine in hemostasis thrombosis and thromboinflammation. J Thromb Haemost 2022;20(07):1535–1549
95 Wang S, Yuan J, Yang J, et al. Advancement of platelet-inspired nanomedicine. Platelets 2018;29(07):690–694
96 Zivkovic M, Gandhi P, Ostergaard H, Olsen E, Rea C, Sorensen B, Faber J, Schutgens R, Bjorn S, Urbanus R. The novel bispecific antibody HMB-001 enhances the haemostatic response in models of Glanzmann Thrombasthenia by targeting FVIIa to activated platelets [abstract]. https://abstracts.isth.org/abstract/the-novel-bispecific-antibody-hmb-001-enhances-the-haemostatic-response-in-models-of-glanzmann-thrombasthenia-by-targeting-fviia-to-activated-platelets/. Accessed June 10, 2023

97 Shapiro AD. Concizumab: a novel anti-TFPI therapeutic for hemophilia. Blood Adv 2021;5(01):279–279
98 Mahlangu J, Luis Lamas J, Cristobal Morales J, et al. Long-term safety and efficacy of the anti-tissue factor pathway inhibitor marstacimab in participants with severe haemophilia: Phase II study results. Br J Haematol 2023;200(02):240–248
99 Mancuso ME, Ingham SJM, Kunze M. Befovacimab, an anti-tissue factor pathway inhibitor antibody: Early termination of the multiple-dose, dose-escalating Phase 2 study due to thrombosis. Haemophilia 2022;28(05):702–712
100 Pasi KJ, Lissitchkov T, Mamonov V, et al. Targeting of antithrombin in hemophilia A or B with investigational siRNA therapeutic fitusiran - results of the phase 1 inhibitor cohort. J Thromb Haemost 2021;19(06):1436–1446