Clinical Reviews & Cases

Thrombocytopenia Treated with Therapeutic Apheresis, and/or Human Monoclonal Antibodies, and/or Thrombopoietin Receptor Agonists

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ABSTRACT

Thrombocytopenia is one of the most common hematologic disorders, characterized by an abnormally low number of platelets from multiple causes. The normal count of thrombocytes is between 150,000 and 450,000/microliter. The clinical expression of thrombocytopenia is a variation from asymptomatic to life-threatening bleeding. The immune thrombocytopenias include the idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), and the post-transfusion purpura (PTP). ITP is a form of thrombocytopenia, caused by autoantibodies, which are mostly accompanied by bleeding. TTP is a rare disease of unclear genesis and a poor prognosis with polyetiological complex, which the kidneys and brain as target organs. PTP is also a rare bleeding disorders caused by alloantibody specific to platelet antigens. Therapeutic apheresis (TA) is accepted as supportive therapy in all immune thrombocytopenia. Further second-line therapies are the human monoclonal antibodies (HMA) and thrombopoietin receptors agonists (TPO-RAs). Besides, the pathological aspects, the first-line and second-line therapies are shown.

Introduction

Thrombocytopenia is one of the most common hematologic disorders, characterized by an abnormally low number of platelets from multiple causes. Thrombocytopenia is an inherited or acquired disease that results in a reduction of circulating thrombocytes. This condition may be asymptomatic or manifests itself in hemorrhagic diathesis with petechial bleeding. The immune thrombocytopenias are a heterogenous group of bleeding disorders with similar hemostatic manifestations but different pathogenic etiologies. There are more than 200 diseases, which include low number of platelet among their symptoms [1].

The normal count of thrombocytes is between 150,000 and 450,000/microliter. The clinical expression of thrombocytopenia varies from asymptomatic to life-threatening bleeding. Different syndromes and diseases are associated with thrombocytopenia. Thrombocytopenia is sometimes a first sign of hematologic malignancies, infectious diseases, thrombotic microangiopathy, and autoimmune disorders, and is a common side effect of many drugs [1].

Idiopathic thrombocytopenic purpura, as a form of thrombocytopenia, is caused by autoantibodies, which are mostly accompanied by bleeding. Its etiology is still most unknown. Fixed antibodies may trigger complement activation. The opsonized platelets are destroyed by phagocytosis. Thrombotic thrombocytopenic purpura is a rare disease of unclear genesis that carries a poor prognosis. Clinically, it manifests itself through high temperature, thrombocytopenia, hemolytic anemia, as well as neurological and renal impairment. It is probably a polyetiological complex with the kidneys and brain as target organs. Post-transfusion purpura is a rare bleeding disorder caused by alloantibody specific to platelet antigens [2].

Platelet transfusions may not be helpful, for example in ITP, heparin-induced thrombocytopenia and TTP. It is important to

recognize the signs and symptoms of these entities. The first-line therapy for thrombocytopenia is with corticosteroids, intravenous immunoglobulins (IVIG), splenectomy, and immunosuppressive agents such as azathioprine, cyclosporin, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, vincristine and vinblastine, or combination of the aforementioned therapies [3]. The second-line therapies for persistent thrombocytopenia includes different methods of therapeutic apheresis, human monoclonal antibodies such as rituximab and others, or a combination with other monotherapies of thrombopoietin receptor agonists such as eltrombopag or romiplostin, The authors try to give an overview of the therapy measurements and the guidelines of the Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) are cited [4,5].

Methods

During the mid-1970s, the therapeutic plasma exchange (TPE) with membrane modules became available. The advantages of this method are a complete separation of the vascular components from the plasma and due to increased blood flow rate higher efficacy. Furthermore, cell damage especially to thrombocytes – occur less using membranes than centrifuge for cell separation [6].

The physicians who have chosen the TA method must be knowledgeable concerning the half-life time, the compartment distribution of pathogenic plasma proteins, and the elimination of other toxic substances and complement components. TA with hollow fiber modules is the most used therapy method in nephrology. Nephrologists have an extensive training in the management of blood purification treatments including vascular access, anticoagulation, volume management and prescription for solute clearance [7]. The renal indications for TPE expand the clinical practice of nephrologists [8].

TPE was explored in the treatment of a variety of autoimmune syndromes. There are only a few prospective controlled trials available, which are of adequate statistical power to allow definitive conclusions to reach regarding the therapeutic value of TA. This drawback reflects, in part, the relative rarity of most of the disorders under investigation. To compensate, many investigators have understandably grouped heterogenous diseases together, often retrospectively, and used historical controls. The latter design is potentially hazardous, given that earlier diagnosis, recognition of milder cases, and improved general care over time may be lost as a benefit TPE. The different TA methods are mentioned elsewhere [8,9].

TPE uses membranes for plasma filtration separation and fractionation. The advantages of membrane plasma exchange include its simplicity to use with blood pumps and no observed white blood cell or platelet loss, compared to centrifuges. The permeability of all these membranes for macromolecules substances reaches a molecular mass of 0.2×10^6 to 0.5×10^6 Dalton. The limit of permeability can reduced by means of changes in the spin process [8].

Cascade Filtration (CF), membrane differential filtration (MDF) seems to be superior to conventional TPE but less effective than adsorption or precipitation techniques [4,5,8]. The CF was developed by Agishi et al. in Japan, 1980, and was the first semiselective technique [8]. Secondary membrane in CF has a cut off approximately one million Daltons. With synthetic secondary membranes and newer types of machines, better effectiveness and selectivity in the separation of blood components can reach: MDF is as safe and effective. Fully automated machines have developed so that continous manual steering of flows and blood pressures in no longer required [6].

Immunoadsorption (IA) was first described by Stoffel et al. in 1981 as LDL-apheresis through sepharose columns coated with LDL antibodies, or other antibodies [6]. The autoantibodies in the plasma after primary separation are adsorbed in the columns onto antibodies. This is a reversible antigen-antibody bond accord based on the principle of affinity chromatography. In the most IA systems, two columns contain 300-320 ml or less volume of sepharose particles. Before one column is saturated with adsorbed autoantibodies (600-800 mL), the plasma flow is switched to the other column; while one column is used for adsorption, the off-line column is regenerated with neutral saline buffer solution, lysine buffer (pH 2.4), and neutral buffer again. In an IA-system with only one column, this column needs no regeneration after the whole treatment. The treated plasma is then mixed with the cellular components of the blood and returned to the patient. The other TA methods such as the heparin-induced LDL precipitation, LDL-adsorption and the LDL hemoperfusion are not used in thrombocytopenia.

Great progress has been made in recent years in developing new treatment options for thrombocytopenia patients, especially in ITP. In addition to TA, human monoclonal antibodies and thrombopoietin agents, combinations of different diagnostic and therapeutic modalities and various therapeutic approaches are the main strategy for difficult cases [1]. HMA therapeutics has been approached for over 30 targets and diseases, most commonly cancer.

There has been a revolution in therapeutics the past 30 years, due to the introduction of protein therapeutics – often termed "biologics" – into routine, mainstream medicine. Biologics are expensive and like all medicines have risks. Their advantage is exquisite specificity due to greater surfaces area binding, resulting in decreased "off-target" effects as compared with most small module drugs. The efficacy and safety of the HMAs have improved in the treatment of various cardiovascular, cancers, respiratory, hematology, autoimmune diseases and infections [10]. Especially rituximab is a novel second-line agent for the treatment of immune thrombocytopenic purpura with encouraged results of some studies.

Thrombopoietin (TPO) is the major physiology regulator of platelet production. It is produced by the liver at a constant rate and cleared from the circulation by TPO receptors on circulating

platelets thereby providing an efficient feedback system regulating platelet production by bone marrow megakaryocytes [11].

The further new second-line drugs for ITP are the thrombopoietin receptor agonists (TPO-RAs). For platelet response, eltrombopag and romiplostim were the best. Romiplostim and eltrombopag have high efficacy and safety as second-line treatments in the short term for adult patients with persistent ITP. Eltrombopag and romiplostim (TPO-RAs) stimulate the platelet and megakaryocyte production. Both substances are approved in the USA and the EU for treatment of different forms of thrombocytopenia [12].

Thrombocytopenia

Thrombotic thrombocytopenic purpura is a rare and life-threatening thrombotic microangiopathy (TMA) syndrome [13]. TTP is a systemic thrombotic illness, which is characterized by the only consistent abnormalities of microangiopathic hemolytic anemia and thrombocytopenia. Recently, TTP has been shown to be associated with a severe (< 5 percentage) deficiency of ADAMTS13 enzyme, which is a protease that cleaves multimers of von Willebrand factor. Idiopathic acquired TTP is associated with antibodies that bind ADAMTS13 and neutralize the protease activity [4]. Severe ADAMTDS13 deficiency appears to be an improvement proximal step in the pathophysiology of TTP. However, some patients with idiopathic TTP have no defect in ADAMTS13 function. Pregnancy, connective tissue disease (e.g., SLE), medications, infection, cancer, and transplantation are all associated with TTP and HUS syndrome [4].

TTP is a medical emergency, since the mortality of untreated patients exceeds 80 % [1]. The mortality is thought to be caused by disseminated microvascular thrombosis, which may provoke ischemic injury and multiple organ failure. Ischemic organ failure can affect all organs, but the brain and heart are typically most affected. Acute kidney injury requiring dialysis and resulting in chronic kidney disease is rare. Central nervous system involvement is often manifested by transient focal neurologic deficits.

The mainstay of treatment is TPE with plasma replacement [2,6,14]. TPE works by removing antibodies against the von Willebrand factor cleaving protease, ADAMTS13. The plasma infused as part of the procedure also provides active ADAMTS13 protease to the patient, further restoring a more physiologic state of von Willebrand factor multimers. Other treatment modalities in non-responders to TPE include immune-suppression, not limited to high dose corticosteroids, and B cell depletion agents (e.g., rituximab). Patients with autoantibodies against ADAMTS13 do not always manifest TTP, and these antibodies alone are not sufficient to demonstrate the impending relapse of the disease. In the case of TTP, it is considered better to avoid platelet transfusion, which should be reserved for patients with clinically significant bleeding, as severe thrombocytopenia itself is not an indication for platelet transfusion. Conversely, platelet transfusion is probably not as dangerous as it was thought to be a decade ago [15].

The majority of acquired TTP in adults are related to an autoimmune disorder where anti-ADAMTS13 antibodies cause that deficiency and subsequent platelet adhesion and aggregation. Bacterial infections, autoimmune diseases, pregnancy, drugs, HIV infection, cancers, organ transplantation are the most frequent clinical conditions associated with TTP [5,16].

The first-line therapy in TTP includes corticosteroids, high dose intravenous immunoglobulin, cyclophosphamide, danazol, vinca alkaloids, and mycophenolate mofetil. The second-line therapy includes first TA, than HMAs, and/or thrombopoietin-receptor agonists [1]. The AAC of the ASFA has given TTP the category I and the recommendation grade 1A for TPE (Table 1) [4,5].

Idiopathic Thrombocytopenic Purpura is an inherited or acquired disease that results in a reduction of circulating thrombocytes. This condition may be asymptomatic or manifests itself in hemorrhagic diathesis with petechial bleeding [17]. The immune thrombocytopenias are a heterogenous group of bleeding disorders with similar hemostatic manifestations but different pathogenic etiologies. ITP caused by autoantibodies, which, in severely progressing cases, are accompanied by hemorrhagic diathesis. ITP is the most common autoimmune hematologic disorder. The etiology is still for the most unknown. The spleen plays an important role, since it not only produces a large part of the antibodies directed against thrombocytes, but also breaks down the damaged thrombocytes. As the antibodies can pass through the placenta barrier, the fetus can also be affected [18]. In more than 60 percent of the patients, part or full remission can be reached with corticoid steroid therapy. Splenectomy and cytostatics are further therapeutic measures. Acute and chronic cases have also successfully treated with high doses of intravenous immunoglobulin of 400 mg/kg BW/day. In recent years, in addition to being treated with TPE, therapy-resistant. The pathophysiological mechanism in ITP is the binding of auto- or alloantibodies to platelet antigens. Fixed antibodies may trigger complement activation [19]. The promised platelets are destroyed by phagocytosis in the macrophage-phagocytic system mediated by the Fc receptors FcRI-III and complement receptors CR1 and CR3. Platelet destruction occurs mainly in the spleen, and accessory spleen, but also in liver and bone marrow. The spleen is a major site of antiplatelet antibody production; therefore, splenectomy is therapeutically very effective. The main antigenic determinants are the platelet membrane glycoproteins GP-Iib/IIIa and Ib/IX [20].

A further mechanism leading to platelet destruction in drug-induced immune thrombocytopenic purpura is the formation of antibodies against neoantigens expressed after adherence of the drug to the RBC membrane [21]. Recently, acquired autoimmune deficiency of a plasma metalloprotease named ADAMTSJB was shown in many cases of ITP [22]. Alloimmunization is the cause of neonatal autoimmune thrombocytopenia, platelet transfusion refractoriness, and post-transplant purpura. The alloantigens are classified on the human platelet antigen (HPA) system [23]. Neonatal immune thrombocytopenia is the platelet counterpart of

hemolytic disease in newborns. QA HPA-Ia-negative is sensitized to HPA-1-positve platelets of the fetus. Alloimmunization (IgG ab > IgM ab) against platelet induced by fetomaternal hemorrhage occurs during a HPA-incompatible pregnancy or after a HPA-incompatible platelet transfusion. In heparin-induced thrombocytopenia, type II immune complexes consisting of antibodies to heparin and platelet factor 4 activate platelets after binding to platelet Fc receptors. Excess platelet factor 4 binds to endothelial glycosaminoglycan, resulting in endothelial damage and thrombi [1]. Heparin-induced thrombocytopenia type I refers to non-immunogenic thrombocytopenia due to heparin-induced aggregation of platelets.

Acute abrupt onset ITP is seen in childhood, and often follows a viral illness or immunization. The majority of children requires no treatment and in 80 – 85 percent of cases the disorders resolves within 6 months. Some 15 – 20 percent of children develop a chronic form of ITP, which in some cases, resembles the more typical adult. Chronic ITP in childhood has an estimated incidence of 4.6 per 100.000 children per year and prevalence of 4.6 per 100.000 children at any one time [24]. This form of ITP affects mainly women of childhood age (female: male: 3:1) Childhood ITP has an incidence of between 4.0 and 5.3 per 100.000 [15].

The diagnosis of ITP based principally on blood count, clinical symptoms, autoimmune profile and other investigation, and on the exclusion of other causes of thrombocytopenia using the history, physical examination. Further investigations are not indicated, blood count and film are typical of the diagnosis of ITP and do not include unusual features that are uncommon in ITP [24]. Platelet associated IgG (PAIg) is elevated in both immune and non-immune thrombocytopenia and therefore has no role in the diagnosis of uncomplicated ITP. In patients refractory to therapy although some patients have shown improvement in platelet counts following eradication therapy, it is worth determining the presence of H. pylori. The first-line therapy comprises oral corticosteroids and IVIG, and immunosuppressive therapy.

The successful use high doses of IgG and anti-D therapy have reduced TA, second-line treatment in these cases [25]. The first-line therapy is splenectomy and high doses corticosteroids, high dose IVIG, intravenous anti-D, cyclosporin A and dapsone. Patients who failed the first-line therapies must be treated with interferon (IFNα), rituximab, campath-1H, mycophenolate mofetil and TA [18]. TA can include remissions in approximately 80 percent of patients with ITP. TA becomes a legitimize option for maintenance therapy in chronic ITP patients, if the application of IgG is not possible due to allergic reactions, Rh-negative status, or splenectomy.

The most important part of TA is to remove anti-platelet antibodies to prevent bleeding by keeping the platelet count above a critical level. The goal of therapy is to obtain sustained remission with a minimum platelet count of over 50.000 platelet/ μl. The measurements of antiplatelet autoantibodies is useful test for determining whether TA is indicated and if so, to assess its efficacy. As some severely progressing cases of ITP do

not respond to steroids and/or high doses of immunoglobulin, immunosuppressive drugs, and biologics, TPE is indicated [24].

As there are only a few controlled studies yet available, it is not possible conclude which form of therapy should be given preference. Thus, in ITP, initial treatment should consist of corticoid steroids, high doses of IgG, and immunosuppressive drugs as mentioned above. Should no significant improvement be observed within one or two weeks (thrombocytes > 80.000 μl), then TA treatment should be commenced immediately. Treatment with to four sections of TPE per month can also perform. The authors recommend TPE with 1 to 1.5--plasma volume a day for 4 days. Have a positive effect in chronic cases. TPE is recommended prior to surgery in acute respectively chronic uncontrollable bleeding [6]. IA with Protein-A was also induced successfully in the treatment of ITP [26].

In the AAC of the ASFA, ITP has the category III and the RG 2c for TPE and IA in refractory cases (Table 1) [4,5]. First-line therapies are oral corticosteroids, IVIG (1-2 mg of prednisolone/kg/day, IVIG at 1 g/kg for 1-2 days), and is anti-RH (d) (50-74 μg/kg [4]. If thrombocytopenia persists or recurs, splenectomy is recommended in adults but is differed to prevent overwhelming post splenectomy infection or allow for spontaneous remission. TPE and IA columns may have been considered in patients with refractory ITP, with life-threatening bleeding or in whom splenectomy is contraindicated. IgG antibodies and IgG-containing circulating immune complexes can be selectively removed by IA with protein-A. The use of this column is contraindicated when the patient is on ACE inhibitors, has a history of hypercoagulability, or thromboembolic events [25]. There are no clear guidelines concerning treatment schedule and duration of treatment. The procedure is generally discontinued when either the patients shows improvement in platelet count > 50 x 10'/L or no improvement after about six treatments. The columns with protein-A is no longer available in the USA but may be available in other countries [4].

Post-transfusion purpura occurs when donor B lymphocytes and dendritic cells migrated as passenger's cells to the recipients system, where they undergo clonal expansion after "homing in" on, and producing alloantibodies to the incompatible HPA allele [27]. PTP is rare bleeding disorder caused by alloantibody specific to platelet antigens. The antibody against the human platelet alloantigen HPA-Ia is responsible for the most of the cases. The majority of affected patients are multiparous women who presumably have been previously sensitized during pregnancy [28]. Blood transfusions rarely have been implicated as the primary cause for alloimmunization in PTP. Thrombocytopenia is usually severe and resolves spontaneously within several weeks. However, patients may develop severe if not fatal bleeding during the course of the disease. The diagnosis is confirmed by demonstrating that the patient´s serum contains antibodies to platelet-specific antigens. Treatments for PTP include IVIG, corticosteroids, and TPE [28]. The treatment is high IVIG (0.4 g/kg BW/day for 2-5 days or 1g/kg BW/day for 2 days) [4]. It is possible acts by Fc receptor blockade of RES. The removal of HPA 1a alloantibodies by TPE

Table 1: Thrombocytopenia and TA (modified after 4, 5).

Apheresis Application Committee of the ASFA 2016, 2019 (4, 5)						
Disease	TA- moda-lity	Cate-gory	Recommen-dation grade	Treated volume (TPV)	Replace-ment solution	Frequency
Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura (TTP)	TPE	I	1A	1-1.5	5% HA- electro-lyte sol.	daily or every other
Idiopathic thrombocytopenia purpura (ITP)	TPE, IA-protein-A	III	2C			
Post-transfusion Purpura (PTP)	TPE, IA-Protein-A	III	2C			

(Category I: accepted for TA as first-line therapy, Category III not accepted for TA, decision should be individualized).

results in a decrease of antibody titer, removal of any unattached HPA-1a antigen, and an increase in platelet count and cessation of bleeding. TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIG therapy is not effective [4]. In the AAC of the ASFA the PTP has the category III with the RG 2C for TPE based on limited data available in the literature (Table 1) [4,5]. TPE can discontinue when platelet count starts increasing (> 20 x 10⁹/L) and non-cutaneous bleeding stops.

Discussion

The first-line therapy of the thrombocytopenia includes glucocorticoid steroids, IVIG, intravenous anti-D immunoglobulin, splenectomy [29]. The second-line therapy includes different methods of TA, different HMAs and/or TRO-RAs [1,3]. The advantage of TA and immunosuppression are described above. TPE is essential, reducing mortality from 90 % to 20 %. Daily TPE is continued until platelet recovery. Corticosteroids used in conjunction with TPE in TTP (17). TA removes an abnormal or unrequired solute or cellular components of the blood [30]. An advantage of TA is the immediately start after diagnosis of thrombocytopenia, the pre-operative therapy or transplantation etc., the management of special form such as heparin-induced thrombocytopenia etc., [30-32].

Despite the recent and underappreciated explosion in the use of monoclonal antibodies as drugs, it remains a significant challenge to generate antibodies with a combination of physicochemical properties that are optimal for therapeutic applications. The most important and underappreciated drug-like antibody properties is high specificity, which is linked to low of-target binding and slow antibody clearance *in vivo* and high solubility and low viscosity *in vitro* [30]. The engineered therapeutic HMAs is as immuno modulators and anti-cancer agents [33]. The shortage potent IVIG and the high costs of polyclonal and monoclonal antibodies making their use restricted in resource-limited countries. Randomized clinic studies for safety and efficacy before putting into regular use are needed.

The current mainstay of the treatment is high IVIG (0.4 g/kg BW/day for 2 – 5 days or 1 g/kg BW/day for 2 days). It possible acts by Fc receptor blockade of reticuloendothelial system [4]. All nonessential transfusions of blood components should be immediately discontinued. In a bleeding patient, transfuse HPA-1a negative platelets, if available. HPA-1a positive platelet transfusion is generally ineffective and likely to stimulate

more antibody production. Patients are also given high dose corticosteroids. TPE is indicated only if IVIG is not effective and severe thrombocytopenia persists. Recombinant FVIIa may be considered in a bleeding patient when HPA-1a negative platelets are not available [4]. Removal of HPA-1a alloantibodies by TPE results in a decrease of antibody titer, removal of any unattached HPA-1a antigen, and an increase in platelet count and cessation of bleeding. TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIG therapy is not effective [4].

Rituximab, the leading and original anti-CD 20 monoclonal antibody, others exist, is widely used in ITP, in various regiments and combinations with other drugs such as with steroids. Rituximab is used intravenous infusions of 375 mg/m² and given once weekly for 4 weeks [1]. The 5-years sustained response to rituximab was shown in 2 studies to be 26 % for children, and 21 % for adults [33-35]. Two studies of one cycle of dexamethasone and rituximab had shown the additive if not synergistic effects of the combination, especially in the newly diagnosed and patients with persistent diseases [34]. However, rituximab targeting B cells as a second-line treatment has about 60 % of patients responding [35]. Rituximab induces a rapid and profound depeltion of B cells but not of plasma cells. The latter also need to be eliminated in organ transplant situation to avoid antibody-mediated rejection [36,37]. Rituximab may not be beneficial due to lower efficacy and higher complications compared with TPO-RAs. Another monoclonal antibody, rozanolixizumab, in patients with ITP was well tolerated, with rate of adverse events such as headaches, hypotension, nausea, epistaxis, abnormal liver function tests, vomiting, and diarrhea. The serum half-life time of the HMA is typically 2-4 weeks in the circulation [38,39]. The role of HMAs is as innovative biopharmaceuticals molecules and as vital components of targeted pharmacological therapies.

Another evaluation of long-term outcomes, as well as cost-effectiveness and impact analysis for both TPO-RAs should be performed to guide health-care policy makers. Further second-line agents are the recombinant human thrombopoietin receptor agonists, such as eltrombopag and romiplostim, which stimulate platelet production [3]. Romiplostim is a peptide TPO-RA which binds to the extracellular domain of thrombopoietin receptor activates JAK-STAT, MAPK and PI3K-AKT pathways, stimulates proliferation and maturation of megakaryocytes, and inhibits

apoptosis of megakaryocytes; resulting in increased platelet production [40]. Eltrombopag is a non-peptide TPO-RA that binds to the transmembrane domain of thrombopoietin receptor and activates the same pathways as romiplostim.

Risk such as severe adverse events (SAEs) and benefit such as efficacy are also considered simultaneously using clustered ranking plot [3]. Romiplostim and eltrombopag have significantly higher efficacy and lower SAEs than rituximab, with romiplostim having a safer adverse event profile than eltrombopag. Puavilau et al. showed some limitations that should be considered. The number of relevant studies and most of either sample sizes were small [3]. Variations in drug dosage and protocol may cause heterogeneity and affect the clinical outcomes. The clinical outcomes evaluated in the included studies were only short-term; these treatments might possible give different results in the long-term [41–43].

Romiplostim and eltrombopag have high efficacy and safety as second-line treatments in the short term for adult patients with persistent ITP. Rituximab may not be beneficial due to lower efficacy and higher complications compared with TPO-RAs. Further evaluation of long-term outcomes, as well as cost-effectiveness and impact analysis for both TPO-RAs should be performed to guide health-care policy makers [3].

Conclusion
The medical process is advancing and will not be stopped. Since the introduction of hollow fiber membranes, exceptional efforts in research and development have been undertaken in the apheresis sector alone, enabling, for example, the introduction of selective separation techniques into everyday clinical practice-techniques that were unsought of at the beginning of the 1980s [17].

The therapeutic apheresis, which includes therapeutic plasma exchange, immunoadsorption, etc., is used since certain years in the treatment of thrombocytopenia with success. More than 80 % of treated patients could be healed with this treatment. This is shown in different studies [17]. The costs of the treatment are known. If HMA or TPO-RAs are not available due to the high costs, TA could be start for the treatment of ITP immediately. Not in every country, HMA or TPO-RAs are available. The costs will be higher as compared to costs of the available other methods.

Rituximab represents an important second-line treatment with about 60 % of patients responding [44]. However, rituximab may not be beneficial due to lower efficacy and higher complications compared with TPO-RAs [3]. Romiplostim and eltrombopag have high efficacy and safety as second-line treatments in the short term for adult patients with persistent ITP [3]. Rituximab may not be beneficial due to lower efficacy and higher complications compared with TPO-RAs. Romiplostim and eltrombopag may yield high efficacy and safety and a combination with other drugs is possible.

More randomized and controlled clinical studies with different

therapeutic shemes, TA and/or HMA, and/or TPO-RAs would be conducted to properly assess the risk: benefit profile of any existing or new treatment by itself or against other options in this setting. Alternatively, given the rarity of both ITP and any potential adverse events associated with a given therapy [45].

Due to the complexity of this condition, management of emergent thrombocytopenic conditions requires an inter-professional team of health care professionals, including specialty-trained nursing, pharmacists, physicians, and specialists working together collaboratively to achieve optimal patient outcomes [46].

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