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REVIEW ARTICLE

Inhibitory hemophilia: contemporary treatment with emicizumab. Considerations for pediatric practice

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ABSTRACT

Introduction. This article provides an overview of current knowledge and global experience regarding the use of emicizumab, with a focus on its specific considerations in pediatric practice. Emicizumab, a monoclonal antibody, operates uniquely compared to other therapies. It has been approved in Moldova since 2019 for preventing bleeding in hemophilia patients. Significant data from clinical studies and accumulated clinical practice provide answers to most questions physicians have when prescribing emicizumab. The article presents recommendations based on current information and global experience to aid decision-making in emicizumab usage. The purpose of this article is to provide information on management tactics for pediatric patients with hemophilia A receiving emicizumab.

Materials and methods. Over 40 publications were reviewed, consisting of recommendations, study results, and observations related to emicizumab use in pediatric patients with Hemophilia A.

Results. In 2017, emicizumab became the first registered non-factorial therapy for Hemophilia A. It was approved for use in treating the inhibitory form of the condition. In 2018, indications for emicizumab were expanded to include patients with the inhibitory form of hemophilia A and severe hemophilia A without inhibitors. Emicizumab is used to prevent bleeding and is not intended to stop an already occurring bleeding. If bleeding has occurred, the patient will need to be prescribed FVIII or bypassing agents. Emicizumab is administered as a loading dose of 3 mg/kg once a week for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg once a week, 3 mg/kg once every two weeks, or 6 mg/kg once every four weeks. The dose is based on the patient's body weight, which needs regular monitoring. If a dose is missed, it should be administered as soon as possible before the next scheduled dose, and the injection schedule should not be altered. Emicizumab can be used in children under one year to prevent bleeding.

Conclusions. Hemophilia, caused by a deficiency in coagulation factors VIII or IX, is a bleeding disorder. The main treatment-related complication in hemophilia patients is the development of inhibitors – alloantibodies that neutralize the procoagulant activity of infused FVIII or factor IX. The reasons why only 20%-30% of Hemophilia A patients develop inhibitors remain a challenge. Emicizumab, a bispecific monoclonal antibody, bridges the gap between activated factor IX and factor X to replace the missing activated factor VIII, thereby restoring hemostasis.

Keywords: emicizumab, hemophilia, factor VIII, factor VIII inhibitor, immune response.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Emicizumab, a type of antibody that binds to both activated FIX and FX, helps compensate for the lack of FVIII in patients with hemophilia A, restoring their ability to control bleeding. Emicizumab is currently registered and available for use in both indications in Moldova as well as in over 95 countries globally.

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The research hypothesis
Identification and analysis of recent findings in the treatment and management of inhibitors in patients with hemophilia A could provide new insights and improvements in future therapeutic approaches.

The novelty added by the manuscript to the already published scientific literature
The article presents a critical review of the existing scientific literature on inhibitory hemophilia, bringing into focus a new perspective on Emicizumab treatment. The manuscript discusses recent findings and empirical evidence, adding to existing knowledge about this complex condition. It also highlights the relevance and therapeutic impact of Emicizumab in the management of inhibitory hemophilia, providing an updated and detailed view on this topic of medical interest.

Introduction

Hemophilia A and B are genetic disorders caused by a lack of blood clotting factors. The first mentions of hemophilia date back to ancient times, and the term "hemophilia" was first documented in 1828. It is often referred to as the "royal disease" because it affected members of the European royal family. The severity of the disease is classified into three degrees depending on the activity of the factor. Approximately 900,000 people worldwide have this condition, with a significant proportion presenting with severe symptoms [1].

Hemophilia has been understood and treated more efficiently over time due to advancements in genetic and molecular biological studies. In the 20th century, treatment options improved significantly, with the development of replacement therapies greatly enhancing patient outcomes. Patients with hemophilia have recorded significant improvements in life expectancy, now averaging 63.2 years. However, those with severe forms of the disease tend to have a shorter lifespan. Despite the progress in hemophilia treatment, challenges persist, such as the burden of treatment and impaired quality of life. Gene therapy may overcome these challenges, but its introduction presents a challenge. Gene therapy involves introducing external DNA into human cells to produce the missing proteins. The main challenge is efficiently delivering genetic material to the target cells and tissues [2, 3].

The standard treatment for Hemophilia A and B has been factor replacement therapy, but it has disadvantages such as frequent intravenous administration and the development of inhibitors. As a result, alternative treatments such as extended half-life products, subcutaneous emicizumab, hemostatic rebalancing agents, and gene therapy have been developed or are being investigated for their efficacy in bleeding control [4, 5].

Despite improvements in hemophilia care, challenges such as treatment burden and impaired quality of life remain. Gene therapy has the potential to overcome these challenges. However, its introduction presents several obstacles. Gene therapy involves inserting foreign DNA into human cells to produce the missing proteins. The main challenge is the efficient delivery of genetic material to target cells and tissues. This is addressed by using viral vectors derived from mammalian viruses, where the viral genes are replaced with a therapeutic gene. Hepatic gene transfer using adeno-associated viral vectors has been successful in both preclinical and clinical studies. In hemophilia A and B, stable levels of factor VIII and factor IX, respectively, were achieved after a single treatment with adeno-associated viral vectors. Lentivirus integration is also being explored as an alternative treatment for hemophilia in children [6]. However, the efficacy of lentivirus integration in humans has yet to be determined. There are several questions about the efficacy and safety of gene therapy, including its use in patients with inhibitors, the likelihood of inhibitors occurring after therapy, and potential safety issues such as thrombosis and carcinogenic effects. It is also unclear how long the effects of gene therapy will last and whether multiple administrations will be needed [7-9].

The main objective of new drugs to treat hemophilia involves the development of recombinant preparations. Various pharmaceutical companies develop these preparations. As the production volume of recombinant blood clotting factors increases, their cost may decrease. Currently, the price of recombinant blood coagulation factor concentrate is higher than that of plasma-based concentrates [3, 10]. However, the development of long-acting preparations allowed increased intervals between administrations. This is especially beneficial for children [6]. Research is also being done to extend the half-life of these drugs. In addition, efforts are being made to develop thermostable preparations that do not require refrigeration for storage. Many current medications can already be stored at room temperature. The development of drugs that can be administered subcutaneously or orally could greatly simplify the treatment process by eliminating the need for venous access. Moreover, the use of small fragments of factor VIII obtained by recombinant technology may help to temporarily reduce inhibitory titers in patients. These fragments can neutralize the inhibitors produced by the patient's antibodies.

For example, in the treatment of hemophilia B, factor IX infusion is usually given every third day or twice a week. However, adolescents often struggle with adherence to this treatment due to the frequency of intravenous injections. In addition, prophylactic treatment in children can be difficult due to limited venous access, which may require the placement of a central catheter. While central access has its advantages, it can also lead to complications such as thrombosis and infection. The ability to undergo prophylactic treatment depends on various factors, including the patient's initial factor deficiency, the severity of bleeding symptoms, the patient's activity and age, and the ease of obtaining venous access [6].

Treatment for the inhibitory form of hemophilia B is the same as for hemophilia A, but with a lower success rate. There are potential problems such as severe allergic reactions and the development of nephrotic syndrome during the induction of immune tolerance. The most effective method for removing inhibitors from hemophilia A is to induce immune tolerance, which involves repeated infusions of factor VIII concentrate to train the immune system to accept the factor. This method has a success rate of 60-80% and allows a normal response to factor therapy and control of bleeding. However, the effectiveness of this method still needs further analysis. The success of inducing immune tolerance depends on the initial level of inhibitors, with better results observed in patients with low or transient inhibitor responses. Patients with high-responder inhibitors or the inhibitory form of hemophilia B have a less promising outlook. Treatment options to control bleeding in inhibitory forms include anti-inhibitory coagulant complex and activated eptacog alfa. A clinical trial showed similar effectiveness of these two preparations in stopping bleeding, but the choice of treatment depends on each patient [5, 10].

Despite improvements in factor therapy for hemophilia, challenges still exist, such as the risk of inhibitor formation and the need for frequent intravenous infusions, which can reduce patient adherence to treatment. Adherence rates for hemophilia treatment range from 50 to 60% [10].

Treatment of hemophilia involves the use of blood clotting factor concentrates, which have greatly improved patient outcomes. These concentrates are obtained from donor plasma or are produced using recombinant DNA technology. There are different types of recombinant FVIII preparations for the treatment of hemophilia, including those with unmodified FVIII polypeptides. The production process for recombinant preparations is long and involves various steps such as gene isolation, viral activation, stabilization, filtration, and concentration.

However, there have been various problems in applying these treatments. For example, nearly half of hemophilia patients in the US were infected with HIV and 80% were infected with hepatitis C [10]. This led to research to improve the safety of plasma concentrates. Today, there are many manufacturers of plasma concentrates that have similar efficacy but differ in purification methods and other factors.

Recombinant concentrates, which are produced using molecular technologies, are safer and cheaper to produce. They are divided into four generations based on the decrease in animal protein used in production. There is also a pig blood plasma concentrate for patients with acquired factor VIII inhibitor. Additionally, concentrates with a longer half-life have been developed to reduce the need for frequent injections.

At the current stage, new treatment methods are being developed, such as monoclonal antibodies like Emicizumab. Emicizumab is a drug used for the prophylactic treatment of patients with hemophilia A and B as well as for the inhibitory form. It is a highly effective humanized monoclonal antibody that inhibits the tissue factor pathway, allowing the generation of factor Xa and thrombin.

The medicine was registered in Moldova in October 2020 and has successfully passed phase II clinical trials. It is administered subcutaneously daily, starting with a dose of 0.15 mg/kg and increasing if necessary [11].

Materials and methods

Initially, the search was conducted using the keywords "Inhibitory Hemophilia" and "Guidelines for Contemporary Treatment in Hemophilia" through publications up to 2023 in the PubMed online database (National Library of Medicine, USA, and National Institutes of Health). After examining the titles, works representing official guidelines for the diagnosis and treatment of Hemophilia with inhibitors and severe Hemophilia without inhibitors were selected. Subsequently, a search was conducted using the keywords "Inhibitory Hemophilia Diagnosis", "Inhibitory Hemophilia Treatment", "Inhibitors in Hemophilia" in the PubMed database for publications from 2020 to 2023. The availability of medicines in Moldova was verified on the website of the Medicines and Medical Devices Agency of Moldova.

Results

Emicizumab is a medicine approved for treating patients with hemophilia A who have inhibitors to factor VIII in over 110 countries worldwide. It is also approved for treating patients without inhibitors in over 95 countries, including Moldova and the European Union. The medicine has been extensively studied in one of the largest clinical research programs for hemophilia A, with eight phase III studies conducted. A bispecific antibody binds to factors IXa and X, proteins involved in blood coagulation. Emicizumab has been approved and included in clinical guidelines for hemophilia treatment in Moldova from 2019 to 2022 [12]. Over 12,500 patients worldwide have received emicizumab in clinical studies and medical practice [1].

Clinical studies have shown promising results. The Emicizumab dosage starts with a loading dose of 3 mg/kg once a week for 4 weeks, followed by a maintenance dose of 1.5 mg/kg once a week, 3 mg/kg every 14 days, or 6 mg/kg every 28 days. Emicizumab is easy to dose and convenient for patients but cannot be used to treat acute bleeding. Thrombotic microangiopathy and thrombosis are the most serious adverse events associated with emicizumab therapy, with 4 cases of thrombotic microangiopathy and 18 cases of thrombosis reported in clinical studies [5].

Results of phase II studies showed a significant decrease in bleeding occurrences by 80-90% compared to the use of eptacog alfa therapy only when necessary [13]. Three cases of blood clot formation were observed during phase III clinical trials, leading to a temporary halt in the study pending further clarification. Additionally, other monoclonal antibody treatments targeting the tissue factor pathway inhibitor, such as PF-06741086 and MG1113, are now entering clinical trials [10].

Throughout the HAVEN clinical trial program, the efficacy of Emicizumab was demonstrated in children, adolescents, and adults with hemophilia A, with or without factor VIII inhibitors. Furthermore, inducing immune tolerance during Emicizumab prophylaxis is a feasible approach in pediatric patients with hemophilia A with inhibitors. After the 4-week loading dose period, Emicizumab concentrations are expected to remain at levels that provide protection against bleeding throughout the dosing interval, regardless of the chosen maintenance dosing regimen, i.e., weekly, every 2 weeks, or every 4 weeks. However, when used with high-dose activated prothrombin complex concentrate, Emicizumab can lead to blood clotting events. Guidelines for managing bleeding episodes in patients using Emicizumab have been issued in the UK, and a group of German specialists has gathered to provide similar guidance [14-17].

Data from HAVEN studies 1 to 4 consistently show the prevention of bleeding throughout the dosing interval, regardless of the chosen dosing regimen. These findings provide additional evidence of sustained efficacy of Emicizumab in all approved dosing regimens to reduce bleeding in individuals with hemophilia A. HAVEN 1 study found that the annual bleeding rate in patients receiving Emicizumab was 5.5 cases in total and 2.9 cases requiring treatment. Vaccination is recommended for these patients according to the national immunization schedule. Vaccination should be done on non-bleeding days and not on the same day as Emicizumab administration. Additional administration of FVIII or rFVIIa (Recombinant activated factor VII) is not necessary before vaccination. Clinical monitoring after vaccination is recommended. Currently, there are no specific studies or recommendations regarding vaccination in patients receiving Emicizumab. Laboratory tests such as aPTT and coagulation tests will be affected by Emicizumab and for 6 months after its discontinuation. Emicizumab therapy does not affect other tests, such as thrombin time. Monitoring Emicizumab concentration is not necessary to assess its efficacy or manage bleeding. Non-compliance with the dosing regimen or development of anti-drug antibodies can lead to a decrease in Emicizumab concentration. Neutralizing antibodies develop in less than 1% of cases and can lead to increased spontaneous bleeding. Consultation with expert centers is recommended if the frequency of spontaneous bleeding increases and the aPTT level is prolonged [18, 19].

Despite the available data, there are still unanswered questions about Emicizumab therapy. These questions include how Emicizumab interacts with other long-term hemostatic medications, whether patients on Emicizumab prophylaxis should continue immune tolerance induction therapy, and how to effectively manage acute bleeding and perioperative support in patients on emicizumab prophylaxis. Although Emicizumab has been proven to significantly reduce bleeding in patients with inhibitors, there is still no consensus on whether patients with inhibitors should undergo immune tolerance induction therapy [20].

Furthermore, when Emicizumab was used in combination with bypass agent prophylaxis, there was a 68% reduction in bleeding rates in the HAVEN 1 study and a 100% reduction in bleeding rates in the HAVEN 2 study. However, it is important to note that in the HAVEN 1 study, three patients developed thrombotic microangiopathy (TMA), and two patients presented with thrombosis when Emicizumab was administered together with a high or frequent dose of activated prothrombin complex concentrate (aPCC). This complication was avoided in the HAVEN 2 study by not combining Emicizumab with a high or frequent dose of aPCC. In the HAVEN 1 study, Emicizumab demonstrated an impressive reduction of 80% in all bleeding, 89% reduction in treated joint bleeds, 92% reduction in treated spontaneous bleeds, and 95% reduction in treated target joint bleeds compared to no prophylactic treatment. Similarly, the HAVEN 2 study showed a significant reduction in bleeding, with a 63% decrease in all bleeding, 94.7% reduction in treated bleeds, 94.7% reduction in treated spontaneous bleeds, 100% reduction in treated joint bleeds, and 100% reduction in treated target joint bleeds compared to absence of prophylactic treatment. The exact role of Emicizumab in combination with current factor VIII replacement therapies and emerging non-replacement therapies is yet to be determined [21-23].

A recent meta-analysis has noted that more research is needed to understand the effectiveness and safety of Emicizumab in younger age groups and those with milder forms of hemophilia A. Additionally; further studies should explore the risk of inhibitor recurrence in patients who have successfully tolerated Emicizumab and transition from other treatments. According to the opinions expressed by experts in this study, more "real-world studies" should be conducted to assess how patients perceive Emicizumab in terms of ease and tolerability to optimize personalized treatment plans [24, 25].

Clinical studies for Emicizumab involved 390 patients. These patients were enrolled in the phase III clinical trial program known as HAVEN1-4. The study program included individuals from various age groups, including pediatric patients up to 12 years old, as well as adolescents and adults aged 12 to 77 years.

HAVEN1 study focused on 109 individuals with inhibitor-type hemophilia A, of which 32 were under 18 years old. The study showed that 63% of these patients did not experience any bleeding incidents throughout the observation period. When comparing the annual frequency of bleeding, it was found that those using Emicizumab had a rate of 3.3, while those using prophylactic treatment had a significantly higher rate of 15.7. This means that Emicizumab reduced the annual bleeding frequency by an impressive 79% compared to prophylactic factor use [26-28].

HAVEN2 involved 88 children and adolescents aged 1 to 15. Among these patients, 72% underwent immune tolerance induction therapy. In the subgroup of 65 patients under 12 years old, the annual frequency of bleeding episodes was 0.3, with a 95% confidence interval ranging from 0.17 to 0.50. Additionally, a significant majority of these patients, especially 77%, did not experience any bleeding episodes requiring therapy. It is noteworthy that 91% of all reported bleeding incidents were attributed to traumatic events [29].

HAVEN4 examined individuals with severe hemophilia A, with and without an inhibitor. This included a small number of children. The study found that the median annual occurrence of joint bleeding (hemarthrosis) throughout the body was zero. However, in the specific joints targeted in the study, approximately 95-98% of patients experienced between zero and three hemarthroses over the year [30].

HAVEN 4 analyzed the use of Emicizumab as preventive treatment every 4 weeks in adults and adolescents with hemophilia A, regardless of the presence of FVIII inhibitors.

Pipe and his colleagues conducted a study involving patients with severe congenital hemophilia A or hemophilia A with FVIII inhibitors who had received treatment with FVIII concentrates or bypass agents. The study took place across multiple locations in Japan, Spain, Australia, Belgium, Poland, and the USA. Participants received subcutaneous Emicizumab every 4 weeks for at least 24 weeks. The study evaluated the pharmacokinetics and safety of Emicizumab in a run-in cohort and the prophylactic efficacy of Emicizumab in maintaining bleeding prevention in an expansion cohort. The study is ongoing and registered on ClinicalTrials.gov.

Between January 30, 2017, and February 27, 2017, a study enrolled seven patients confirming the safety and expected effects of a drug regimen. This led to the expansion of the study, enrolling an additional 41 patients. The annual rate of treated bleeding was 2.4, with over half of the patients not reporting treated bleeding, and the majority reporting from zero to three treated bleedings. The most common side effect was injection site reaction. There were no blood clotting events or development of antibodies neutralizing the drug. Overall, the drug showed effective bleeding control and could enhance care for those with hemophilia A.

In the clinical studies HAVEN 1-4, a small percentage of patients developed antibodies to Emicizumab, with a few experiencing a decrease in drug efficacy. However, these antibodies did not increase the risk of inhibitor development and did not influence the efficacy of other hemophilia treatments. The most common adverse events associated with Emicizumab were reactions at the injection site, headaches, and joint pain. Thrombotic events and thrombotic microangiopathy (TMA) were rare but serious complications requiring immediate hospitalization. Cases of TMA were more likely to occur in patients receiving high doses of activated prothrombin complex concentrate (APCC) alongside Emicizumab, while rFVIIa did not trigger TMA. Thrombotic events were also reported, but the risk was similar to that in the general male hemophilia population [25, 31].

HAVEN 5, conducted by Renchi Yang, aimed to evaluate the efficacy and safety of Emicizumab in participants from the Asia-Pacific region aged 12 and above, with severe hemophilia A without FVIII inhibitors or any severity of hemophilia A with FVIII inhibitors. Participants were randomly assigned to one of three groups: Emicizumab 1.5 mg/kg once a week, Emicizumab 6 mg/kg every 4 weeks, or no prophylaxis. The primary objective of the study was the annualized bleeding rate (ABR) for treated bleeding, compared between individuals receiving Emicizumab prophylaxis and those without prophylaxis. Secondary objectives included ABR for target joint treated bleedings. Safety was also assessed throughout the study. Based on the study results, it can be concluded that both Emicizumab dosage regimens (1.5 mg/kg once a week and 6 mg/kg every 4 weeks) demonstrated effective bleeding control in the studied population. Additionally, Emicizumab was well-tolerated, and its use as prophylaxis could improve outcomes for people with hemophilia A. The most commonly reported adverse event in the study was upper respiratory tract infection, occurring in 14 out of 56 participants (25.0%) receiving Emicizumab and in 2 out of 14 participants (14.3%) without prophylaxis. No thrombotic events, thrombotic microangiopathies, or deaths were reported during the study period [32].

HAVEN 6 evaluated the safety and effectiveness of Emicizumab prophylaxis in individuals with non-severe hemophilia A without FVIII inhibitors. The study involved 72 participants receiving Emicizumab treatment for at least one dose. Participants experienced some adverse events, but none were severe enough to discontinue treatment. The study found that Emicizumab was effective in reducing bleeding episodes, with an annual bleeding rate of 0.9 for treated bleedings. Overall, the study concluded that Emicizumab is a valuable treatment option for individuals with non-severe hemophilia A without FVIII inhibitors. New data from the HAVEN 6 study show that Emicizumab Roche is effective and safe for patients with moderate or mild hemophilia A. The study found that 66.7% of participants had no treated bleeding episodes. The updated data also confirm the favorable safety profile of Emicizumab, with no new safety signals identified. It is noteworthy that there is limited information and recommendations for the treatment of moderate or mild forms of hemophilia A, which can lead to delayed or incorrect diagnosis of bleeding episodes. Emicizumab is approved for the treatment of hemophilia A, with or without FVIII inhibitors in many countries [33-35].

The use of Emicizumab as a preventive treatment in individuals who have not been previously treated is still under discussion. It is unclear what the occurrence and effects of FVIII inhibitors are in this situation. Various efforts are being made to address this issue. A study, named HAVEN 7, is currently enrolling participants to evaluate early prevention with Emicizumab in children under 12 months with hemophilia A without inhibitors. Another study compares inhibitor data in individuals who have not received treatment before and who undergo preventive treatment either with an extended half-life recombinant FVIII concentrate or with Emicizumab. A third study also evaluates inhibitor data in individuals receiv-

ing preventive treatment with Emicizumab and a low dose of simoctocog alfa, a recombinant FVIII concentrate. Both studies are currently recruiting participants [36, 37].

The inclusion of Emicizumab in both international and national treatment guidelines for patients with hemophilia A became possible due to the positive results observed in clinical studies. In the latest edition of the World Federation of Hemophilia guideline, it emphasizes that Emicizumab prophylaxis can effectively prevent hemarthrosis, spontaneous bleeding, and interventional bleeding in individuals with severe hemophilia A without inhibitor antibodies. These findings underscore the significant potential of Emicizumab as a treatment option to improve the quality of life and reduce the risk of bleeding episodes in this patient population [38].

A study was conducted to examine bleeding patterns in 70 hemophilia A patients taking Emicizumab for over 18 months. The study found that the occurrence of spontaneous and traumatic bleeding did not significantly differ at different time points during the study. Traumatic bleeding was most commonly caused by hemarthrosis and cranial trauma, while spontaneous bleeding was most commonly caused by hemarthrosis. The study also found that the chance of bleeding during Emicizumab treatment increased with age. These findings suggest that older patients may still be exposed to the risk of bleeding despite Emicizumab therapy. This information may be useful for physicians when counseling patients and planning treatment [39].

Previous reports have discussed the efficacy, safety, and pharmacokinetics of Emicizumab, but there is limited long-term data available. The study conducted by Callaghan *et al.* (2021) examined data from 401 people with hemophilia A, who participated in four phase 3 studies to assess the long-term efficacy, safety, and pharmacokinetic profile of Emicizumab. The data showed that over an average duration of 120.4 weeks, the annual bleeding rate decreased and stabilized to less than one. Most participants did not experience bleeding episodes or had very few bleeding episodes, and bleeding in target joints significantly decreased. Emicizumab was well tolerated, with no new safety issues identified [25, 40].

A study conducted by Hankil Lee examined the cost-effectiveness of Emicizumab prophylaxis in patients with hemophilia A inhibitors and factor VIII in Korea [41]. These patients frequently experience spontaneous bleeding and require costly treatments to control bleeding. The study found that Emicizumab prophylaxis, compared to on-demand treatments, significantly reduced bleeding rates, improved quality of life, and lead to cost savings. The findings suggest that Emicizumab prophylaxis is a highly beneficial treatment option for these patients. A study conducted in February 2020 evaluated the cost-effectiveness and budget impact of using Emicizumab prophylaxis in patients with hemophilia A and inhibitors. Emicizumab was proven more efficient and economical compared to other prophylaxis methods. The use of Emicizumab also led to a significant reduction in healthcare costs. This study suggests that Emicizumab is a cost-effective and sustainable treatment option for patients with hemophilia A and inhibitors. In comparison to prophylaxis with bypassing agents, Emicizumab reduced direct and indirect costs, resulting in cost savings for the National Health System and society in Spain [42, 43].

However, another study documented the cost-effectiveness of prophylactic Emicizumab compared to prophylactic recombinant factor VIII in patients with mild or moderate hemophilia A without inhibitors in the United States. The study found that currently, Emicizumab is not cost-effective in this patient population, and its price should decrease by more than 35% to become cost-effective [44]. Similarly, a study from Canada examined the effectiveness and cost of Emicizumab for severe hemophilia A. The study found that the cost of Emicizumab was not justified based on the benefits it provided compared to other treatments. The price of Emicizumab should be reduced to make it more cost-effective. Although Emicizumab has been shown to reduce bleeding, there is not enough evidence to directly compare it with other treatments. The reimbursement demand for Emicizumab does not match the population it is intended for, adding uncertainty to its cost-effectiveness [45].

The effectiveness of Emicizumab has been compared to Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in many studies. rFVIIIFc has proven its efficacy and is cost-effective compared to Emicizumab, providing clinicians with a viable treatment option to improve health outcomes for adults and adolescents with hemophilia A in the UK [46]. Similar results were observed in a study conducted by Klamroth *et al.* [47]. The authors aimed to compare the effectiveness of two treatments, rFVIIIFc and Emicizumab, for patients with hemophilia A without inhibitors.

Discussions

In the last 80 years, significant progress has been made in the treatment and quality of life for hemophilia patients. The focus has shifted from simply preventing bleeding and death to improving overall independence and integration into society for patients. Although new treatment methods have been successful, the standard therapy of intravenous infusions of factor concentrates still has limitations affecting patient adherence. Inadequate disease control can lead to joint damage, especially in patients with inhibitors. However, the development of new treatments and gene therapy offers hope for further improvements, but their long-term performance and safety must be carefully evaluated.

The health of children and adolescents is a national priority due to the demographic crisis. The focus is on addressing socially significant diseases such as cancer and blood disorders, which are the second leading cause of death in children in Moldova. To ensure the best possible hematological care for children and adolescents, specific indicators measuring the quality of care in terms of structure, process, and outcomes need to be utilized. Unfortunately, these indicators have not been established or implemented nationally. Therefore, to address the challenges associated with specialized hematological care, new therapeutic technologies and research must be introduced [47].

In the last eight decades, there have been significant and monumental changes in approaches, evaluation techniques,

therapy availability, and overall quality of life for people with hemophilia. Initially, the main goal was simply to prevent patients' deaths from excessive bleeding. However, the focus has now shifted towards improving the quality of life for hemophilia patients and ensuring their complete independence and integration into society. The goal is to eliminate any exceptions from this standard and allow every child with hemophilia to live a life similar to those without this condition. Despite significant progress with the introduction of new treatment methods, it is important to note that the "gold standard" of therapy remains intravenous infusions of factor concentrates, despite its limitations that may hinder patient adherence to this form of treatment. Inadequate disease control can lead to recurrent hemarthrosis and, ultimately, the development of resistant arthropathy in the affected joints. The issue of patients with inhibitors represents a unique challenge, as existing therapy is often incredibly challenging to tolerate and does not always yield successful results. However, the emergence of new drugs with a completely new mechanism of action and more convenient administration methods, along with the ongoing development of gene therapy, offers hope for a significant improvement in the quality of life for people with hemophilia. However, it is crucial to carefully analyze the long-term efficacy and safety indicators of these new treatments.

Patients with hemophilia A with inhibitors currently have unmet needs, such as the requirement for intravenous substitution therapy and the burden of prophylactic treatment. Emicizumab is a monoclonal antibody designed to address these needs and has undergone phase III clinical trials in both adolescents and adults as well as children.

Continued real-world experience with Emicizumab has shown that it is safe and effective in treating children, adolescents, and adults with hemophilia. The launch of Emicizumab takes place in over 100 countries, including low- and middle-income countries, through the World Federation of Hemophilia's Humanitarian Aid Program. Various pharmacokinetic and dosing tools are available to customize treatment and minimize medication waste. Long-term clinical studies and real-world monitoring have further confirmed the safety and efficacy of Emicizumab in children and adolescents. Ongoing clinical studies address additional questions about the use of Emicizumab with other therapies and the recurrence of inhibitors. In conclusion, Emicizumab is widely used globally and can be customized based on individual pharmacokinetic needs, with consistent outcomes observed in different age groups.

Studies have shown significant reductions in bleeding and joint events when Emicizumab is used compared to no prophylaxis. Emicizumab has also demonstrated reductions in bleeding rates in patients on bypassing agent prophylaxis. However, in the analysis of some studies, cases of thrombotic microangiopathy and thrombosis have been reported when Emicizumab was used with a high or frequent dose of activated prothrombin complex concentrate. No patient developed these complications when the combination was avoided. The use of Emicizumab is currently being studied in patients without inhibitors and in combination with other therapies for hemophilia A, but its role with current factor VIII replacement therapies and non-replacement therapies is still uncertain.

Before using Emicizumab, healthcare professionals must have experience in treating hemophilia A and be familiar with the mechanism of action, administration, and potential side effects of the drug. Emicizumab is used to prevent bleeding, not to treat it, so patients must have other medications on hand to stop bleeding if necessary. In general, not all bleeding episodes occurring with Emicizumab prophylaxis require treatment.

Preventing hemarthrosis is an essential part of hemophilia treatment, as it can lead to joint damage and disabilities. Emicizumab has been shown to effectively protect against bleeding and reduce the frequency of hemarthrosis in patients with severe hemophilia A. It is important to initiate Emicizumab therapy under the supervision of an experienced physician, and patients should receive training in the proper injection technique. If patients have long-term venous access systems, they should be removed within one month of starting Emicizumab treatment. Patients and caregivers should be educated about the differences between Emicizumab and previous treatments and instructed in the administration of other hemophilia treatments in case of bleeding. Patients with the inhibitory form of hemophilia A should be aware of the increased risk of thrombotic events when using certain coagulation complexes with Emicizumab. For patients without inhibitors, Emicizumab therapy can be initiated without prior preparation. Patients should also be taught how to manage bleeding or trauma and should seek medical help in such cases. It is recommended that all patients receiving Emicizumab have an emergency or urgent surgical information card.

Conclusions

Alloantibodies against factor VIII develop in 25 to 50% of children with severe hemophilia A, as well as in a small percentage of children with mild or moderate hemophilia A. In patients with hemophilia B, alloantibodies appear in only 1 to 3% of individuals with the severe form.

During the initial administration of products containing FVIII, patients with hemophilia A may develop a proinflammatory immune response with the synthesis of anti-FVIII IgG1, which lacks inhibitory activity against FVIII.

Most patients with inhibitory Hemophilia A with high titers attempt inhibitor elimination using one of several immune tolerance induction (ITI) regimens. ITI has been less successful in patients with hemophilia B and inhibitors compared to those with hemophilia A.

Emicizumab is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure. Emicizumab bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis. It has no structural relationship or sequence homology to factor VIII and, as such, does not induce or enhance the development of direct inhibitors to factor VIII.

For the treatment of bleeding episodes in patients with high-titer inhibitors (≥ 5 Bethesda units), a prothrombin complex concentrate (PCC) (preferably an activated PCC [APCC]), recombinant factor VIIa, or porcine factor VIII can be used.

Competing interests

None declared.

Authors' contributions

VT and AD had a crucial role in the collection and analysis of empirical data, laying the foundations for the central argumentation of the paper. Their meticulous work allowed not only to interpret the data in a new and innovative way, but also to integrate it into the wider context of specialist research. GE, AD on the other hand, focused on building the theoretical framework, exploring, and synthesizing the existing specialized literature. All authors have read and approved the final version of the manuscript.

Ethical statement and patient consent

No approval was required for this study.

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