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Review Article

Advancements in the diagnosis and management of haemophilia from traditional therapies to gene editing: a narrative review

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ABSTRACT

Hemophilia is an X linked rare hereditary bleeding disorder, caused by deficiencies in clotting factors VIII (Hemophilia A) or IX (Hemophilia B). Its diagnosis and treatment —from conventional factor replacement therapy to advanced gene-editing techniques. The intent is to present a narrative review about the evolution of diagnosis and treatment of hemophilia. Literature between 2012 and 2024 was cross-checked by using the keywords “Hemophilia A”, “Hemophilia B”, and “gene therapy” in the search fields of PubMed, EMBASE, the Cochrane Library, Web of Science, and Google Scholar. Only studies related to human subjects with Hemophilia A or B who received diagnosis or treatment were included; English was the only accepted language. The review included case-control studies, cohort studies, randomized controlled trials, systematic reviews, and meta-analyses. Alternative medicines, animal experiments, and non-original research were among the exclusion criteria. The articles were screened for relevance and consistency using Rayyan software by two impartial reviewers. As a result of reviewing the literature, the study was based on 13 relevant studies. Firstly, gene therapy allows the body to naturally produce clotting factors, successfully restoring IX levels in hemophilia B patients. Secondly, non-factor therapies, such as Emicizumab, provide modern alternatives that enhance clotting without traditional factors. Finally, emerging technologies like CRISPR/Cas9 provide opportunities for permanent and personalized cures. This review highlights the transformative potential of gene therapy, which enables the body to produce clotting factors via adeno-associated viral vectors, addressing the limitations of traditional therapies. Integrated care through multidisciplinary teams is essential for improving outcomes.

Keywords: Hemophilia A, Hemophilia B, Bleeding disorder, Hematology, Genetic

INTRODUCTION

Hemophilia is a genetic X-linked condition characterized by a deficiency of clotting factors that are crucial for the process of blood coagulation. Hemophilia A arises from an insufficiency of coagulation factor VIII (FVIII), whereas Hemophilia B is attributed to a deficit in factor IX (FIX), these are the two types of Hemophilia. The severity of hemophilia is determined by the levels of these clotting factors. Hemophilia mainly affects males in particular, the most common type, hemophilia A, affects about 1 in 5,000 to 10,000 males, and hemophilia B affects about 1 in 34,500 males.[1,2] Individuals who have severe hemophilia typically exhibit spontaneous bleeding or bleeding resulting from trauma most often into soft tissues, muscles, or joints. This could also result in life-threatening forms of hemorrhage such as intracranial hemorrhage. Typically, individuals with mild or moderate

hemophilia have bleeding resulting from trauma or medical procedures.[3] Initially, it was thought that the bleeding in hemophilia was due to either platelet disorder or weak blood vessels. Nevertheless, in 1937, Taylor et al, discovered that the use of plasma derivatives was a good way to manage coagulation. This, in turn, gave rise to the recognition of the problems with factor VIII and factor IX in 1944. This knowledge gave precise treatment and diagnostic methods.[4]

In the 1950s and 1960s, the methods used such as whole blood or plasma were not adequate, which caused the death rate to increase. In the 1970s, the use of lyophilized plasma concentrates and home therapy enhanced the control of bleeding and diminished joint damage. The decade of the 1980s also saw the advancement of recombinant FVIII and FIX which offered treatments that were safer and more effective.[4] The last 15 years have been termed a "new golden era" in the treatment of hemophilia. Life expectancy of an average patient is now close to that of the general population in high-income countries. Bypassing agents such as activated prothrombin complex concentrates (APCC) and recombinant activated factor VII (rFVIIa) have significantly changed bleeding control in individuals with inhibitors. rFVIIa has shown particular efficacy in managing bleeding.[4]

Bioengineering inventions have opened up vast opportunities for modern, interesting, stable therapies, primarily monoclonal antibodies, mimicking FVIII, and FIX, gene therapy using viral vectors or DNA plasmids, and gene editing methods such as CRISPR/Cas, all destined to possibly being capable of curing hemophilia. Problems with adeno-associated virus (AAV) vectors continue, as pre-existing immunity to certain AAV serotypes could increase their ineffectiveness in certain individuals. The CRISPR/Cas system is an intriguing option that holds the promise of a permanent solution.[5]

Even though the advancement of hemophilia diagnosis and treatment, obstacles still exist in overcoming long-term complications and ensuring that equitable access to health care, especially in settings with limited resources. Although gene editing and other novel therapies hold the promise of a cure, their long-term safety, effectiveness, and ethical implications need to be studied further.

This review discusses the development of hemophilia diagnosis and treatment, starting from early blood transfusions to gene therapies, focusing on challenges that persist and the need for continued innovation to improve patient outcomes and work toward a definitive cure.

METHODS

The aim of this narrative review is to identify the innovations in the diagnosis and management of hemophilia by reporting the shift from orthodox treatment methods to advanced novel ones like gene therapy.

PubMed, EMBASE, Cochrane Library, Web of Science, and Google Scholar were searched for literature published between the years 2012 to 2024, and Studies limited to the English language were included. This search strategy was utilized: (hemophilia OR bleeding disorders) AND (diagnosis OR management OR gene therapy OR gene editing OR traditional therapies) AND (clotting factors OR gene transfer OR treatment outcomes). The studies considered for this review had participants who were human patients who were diagnosed with either hemophilia A or hemophilia B and some diagnostic or treatment interventions were done. The review comprised of an extensive variety of study types including randomized controlled trials, cohort studies, case control studies, systematic reviews, and meta-analyses. Exclusion criteria included non-original research, animal studies or research looking at alternative therapies including those focused on hemophilia gene editing. To promote consistency of this selection process, two independent reviewers screened titles and abstracts in Rayyan software.

Then, the full articles were evaluated for relevance and eligibility, and discrepancies were resolved through discussion and consensus between the reviewers. This comprehensive synthesis provides an overview of how innovations in gene therapy and gene editing are transforming the landscape of hemophilia care, in comparison to conventional factor replacement therapies.

Etiopathogenesis

Hemophilia is an X-linked recessive disorder that disrupts blood coagulation and results in excessive or spontaneous bleeding. It is caused by an absence of clotting proteins VIII (Haemophilia A) or IX (Haemophilia B). Males are typically more affected because they only have one X chromosome, while females are typically carriers unless both X chromosomes contain the mutation. One significant issue with replacement therapy is the possibility of immunological responses. This may lead to the development of inhibitors or neutralizing antibodies against the injected clotting factor. About 30% of people with hemophilia A and 3% of patients with hemophilia B may develop these inhibitors.[6]

Clinical presentation

The joints and muscles are the primary sites of spontaneous bleeding, which can cause severe and long-term damage to the musculoskeletal system and disability if left untreated. Moreover, uncontrolled bleeding occurs in conjunction with trauma and surgical procedures.[7]

Diagnosis

Hemophilia is diagnosed by laboratory testing to determine the precise clotting factor deficiencies and clinical history, including bleeding events that occur spontaneously or as a result of trauma. In addition to

having an extended activated partial thromboplastin time (aPTT), patients with hemophilia typically have normal fibrinogen, platelet counts, and prothrombin times (PT). While factor IX deficit confirms hemophilia B, factor VIII insufficiency confirms hemophilia A.[8]

Treatment

Conventional Medicine Traditionally, hemophilia is treated by making an intravenous infusion of the deficient clotting factor (factor VIII in hemophilia A & factor IX in hemophilia B). Although they are effective in preventing the risk of bleeding, constant infusions are quite bothersome while some patients form inhibitors that make the treatment even more complicated. Non-factor therapies such as emicizumab perform similar functions to factor eight by enhancing the clotting process and lowering the treatment impacts. These therapies are helpful in people with and without inhibitors and instead of using factor replacement, these therapies can be used instead.[9,10]

Gene Therapy Viral vectors such as the adeno-associated viruses (AAV) can alleviate the deficiencies associated with hemophilia and so they provide a permanent solution, these viruses enable the body to create its own clotting factors and this reduces the number of infusions a patient might require. With these gene therapies for example, Etranacogene Dezaparvovec has been effective in restoring the concentration of factor IX in B hemophiliacs. Regional Accessibility It is important to note there is a variation in the global access of advanced therapies. For instance, Turkey is one of the countries that is trying to adopt gene therapy in the usual treatment while dealing with issues such as finances and the availability of clinics.[3,11]

Malignant potential

Clotting factors derived of plasma were once feared due to the risk of HIV or hepatitis transmission which could have led to liver cancer, however, the use of recombinant clotting factors has reduced such risks significantly.[4] Even though Gene therapy has shown promising results, there exists a hypothetical risk where insertional mutagenesis could occur which would signal the activation of viral oncogenes. Though these risks are gone today by incorporating new techniques, the use of these new therapies would still require long-term monitoring of the subject's safety.[12]

Immunosuppressive treatments are sometimes a necessity for patients suffering from cancer, however, there is a risk associated as the weakened immune system would not be able to eradicate impacted malignant cells. Furthermore, routine management and monitoring is required to reduce such potential risk.[13] Such considerations stress on the need and importance of more reliable and effective hemophilia treatments while ensuring that the patient's safety and long-term efficacy of the treatment is ensured.

Management

Comprehensive management of hemophilia is further enhanced via comprehensive care centers where multidisciplinary teams tackle physical, psychological, and social aspects of disease, thus enhancing quality of life for the patients. Clotting factors, which are introduced into the body periodically, reduce the chances of internal bleeding or even injury to the joint. Treatment can always be more effective when it has a formulated strategy as per the individual.[2,6]

The principles underlying the field of pharmacogenetics and pharmacokinetics have contributed towards the purposes of pharmacotherapy by allowing for custom made approaches that best suits various requirements.[2] The treatment of hemophilia is being enhanced using telemedicine by having follow-ups and consultations while the patient is away. These technologies also increase the availability of service in areas that have been neglected in the past.

Transgenic approaches using techniques such as CRISPR/Cas can transform how hemophilia is treated through the alteration of genes that cause the disease in the first place. These can be a game-changer in the long run as they offer permanent solutions whilst remaining still in experiments.[9,10,12]

CONCLUSION

In conclusion, hemophilia is a genetic X-linked disorder characterized by a deficiency in clotting factors VIII and IX, primarily affecting males and leading to spontaneous or trauma-related bleeding. This review highlights advancements in the diagnosis and treatment of hemophilia, emphasizing the ongoing challenges and the need for continuous innovation to improve patient outcomes and pursue a definitive cure.

The findings from the included studies reveal that gene therapy has the potential to be a transformative approach, allowing the body to naturally produce clotting factors through adeno-associated viral vectors. This method not only overcomes the limitations of conventional therapies, such as high costs and the risk of developing inhibitors, but also paves the way for permanent and personalized treatments utilizing technologies like CRISPR/Cas9. Additionally, emphasizing integrated care through multidisciplinary teams is essential for enhancing overall patient outcomes.

To maximize these advancements, we recommended to invest in gene therapy research, promote multidisciplinary collaboration, and raise awareness of emerging treatment options. Furthermore, developing cost-effective solutions and encouraging participation in clinical trials will significantly improve the management of hemophilia, providing comprehensive support and fostering better well-being for patients.

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