Chapter

Wiskott-Aldrich Syndrome

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Abstract

The Wiskott-Aldrich syndrome (WAS) could be a rare X-linked primary immunodeficiency disorder characterized by recurrent infections, eczema, and bleeding following thrombocytopenia. Despite the rarity of this syndrome, today our understanding of the cellular and molecular basis of the pathogenesis of this disease has increased and it's well established that this disorder encompasses a wide range of clinical disorders including immunodeficiency, atopy, autoimmunity, and cancer. Wiskott–Aldrich Syndrome protein (WASP) mutations are located throughout the gene and inhibit or regulate the conventional function of WASP. Thus classic WAS occurs when WASP is absent, X-linked thrombocytopenia when mutated WASP is expressed, and X-linked neutropenia when missense mutations occur within the Cdc42-binding site. Developments within the use of diagnostic tools, supportive care, and advances in allogeneic hematopoietic cell transplantation have remarkably reduced the mortality related to this disorder. Besides, gene therapy has provided optimistic perspectives on the treatment approaches of those patients.

Keywords: Primary immunodeficiency, Wiskott-Aldrich Syndrome, X-linked thrombocytopenia, X-linked neutropenia, Hematopoietic cell transplantation, Gene therapy

1. Introduction

Wiskott-Aldrich syndrome (WAS) is a rare X-linked recessive disorder that is defined in three categories consist of severe immunodeficiency, thrombocytopenia, and eczema. Moreover, high frequency of lymphomas (mainly B cell origin), susceptibility to autoimmune diseases, recurrent infections, variable defects in B and T-lymphocyte function ,and bloody diarrhea are classified as other symptoms [1]. A genetic mutation in the WAS gene encoding Wiskott-Aldrich syndrome protein (WASp) affecting the immune system and leads to immunodeficiency. There is broad-spectrum depending on gene mutations ranging from severe phenotype (Classic WAS) to mild ones which consist of X-linked thrombocytopenia (XLT) and X-linked neutropenia (XLN) [2, 3]. The purpose of this chapter is to discuss WASp function, clinical and pathological manifestations associated with mutations of the WAS gene as well as a comprehensive review of WAS clinical diagnosis and treatment methods and their complications. In addition, a range of therapeutic approaches will be discussed, including the use of allogeneic hematopoietic stem cell (HCT) transplantation and gene therapy.

2. Etiology

Wiskott-Aldrich syndrome is caused by mutations of the gene WASP (WAS protein) involved in actin polymerization, cellular signaling, cytoskeletal rearrangement, and immunological synapse formation. These mutations cause changes in protein structure by different mechanisms and lead to different phenotypes of this disease [1, 2].

3. Epidemiology

It has been estimated that one in every 100,000 male births leads to Wiskott-Aldrich Syndrome, and in families without a history of the disease, the average age of diagnosis is 24 months [4, 5]. In the United States, the estimated incidence of WAS is one in 250,000 male births. Whereas WAS still is a rare disease, it is more common than other immunodeficiency syndromes such as hyper-IgM syndrome or SCID which have an estimated incidence of about one in 1,000,000 live births. It is thought WAS accounts for 1.2% of all inherited immunodeficiencies in the United States [6]. Up to now, the impact of any ethnic or geographical factor on its incidence has not been reported. Because of misdiagnosing of mild cases, these conditions may be presumed as idiopathic thrombocytopenia purpura [4].

4. Clinical and pathological manifestations

4.1 Incidence and clinical phenotypes

The incidence of the classic WAS phenotype has been estimated at 1 in 100,000 individuals. Based on clinical manifestations, WAS-XLT commonly is presented at birth and consists of bruising, bloody diarrhea as well as petechiae. Excessive bleeding consequent circumcision can be considered as an early diagnostic sign. Furthermore, during infancy and childhood, eczema is a frequent manifestation of patients with classic WAS. Small platelet and thrombocytopenia are the most reliable finding in WAS and XLT phenotype. A variety of infections such as bacterial pneumonia, skin infections as well as otitis media with drainage of mucoid material are common complaints. XLT patients are less likely to have problems such as eczema and infection and oftentimes are misdiagnosed with Idiopathic thrombocytopenic purpura (ITP). Patients with X-linked neutropenia caused by missense mutations in the Cdc42-binding domain are affected at birth. However, their symptoms do not resemble those of classic WAS or XLT. Through a simple scoring system, we have delineated different clinical phenotypes (**Table 1**).

4.2 Thrombocytopenia

It is the foremost common finding present at the time of diagnosis and appears at birth. However, the severity is variable. Approximately 50% of patients with WAS will have severe Thrombocytopenia with a platelet count<20,000/μL. Furthermore, the severity of Thrombocytopenia has a close relationship with bleeding. Bleeding events occur in >80% of WAS patients. These bleeding complications consist of non-life-threatening (e.g, ecchymosis, hematemesis, epistaxis, petechiae, etc.) and or life-threatening (eg, gastrointestinal and intracranial hemorrhage). life-threatening bleeding happens in 30% of patients. However, intracranial hemorrhage occurs in exactly 2% of cases. Although Megakaryocyte numbers are typically

	WAS	XLT	IXLT	XLN
Phenotype				
Thrombocytopenia	+	+	(+)	-
Small platelets	+	+	+	-
Eczema	+/++/+++	-/+	-	-
Immune deficiency	+/++	-/(+)	-	-
Infections			-	+*
Autoimmunity and/or malignancies	Frequent	Possible	-	-
Congenital neutropenia	-	-	-	+
Disease scores	3,4, or 5	1,2, or (5)†	<1	0
WASP expression	Absent or truncated	Present, reduced quantity	Present, normal quantity	Present
Treatment				
IVIG	Yes	No (with exceptions)	No	No
HSCT	Yes at an early age	Might be considered if there is a sibling donor	No	?
Splenectomy	No	Might be considered‡	No	No

IXLT, Intermittent XLT; HSCT, hematopoietic stem cell transplantation; XLN, X-linked neutropenia.
Scoring system: -/ (+), absent or mild; -/+, intermittent thrombocytopenia; (+), mild, transient eczema or mild, infrequent infections not resulting in sequelae; +, thrombocytopenia, persistent but therapy-responsive eczema, and recurrent infections requiring antibiotics and often IVIG prophylaxis; ++, eczema that is difficult to control and severe, life-threatening infections.
**Infections typical for neutropenia.*
†Patients with XLT with a score of 1 or 2 might progress to a score of 5. Incidence of autoimmunity and malignancies are less in XLT than in WAS.
‡Splenectomy results in increased platelet numbers and reduced bleeding but causes a marked increase in sepsis, requiring continuous antibiotic prophylaxis.

Table 1.
Clinical phenotype associated with mutations of the WASP gene [acc.19].

normal in patients with WAS, platelet formation changes into abnormal. It should be noted that the role of anti-platelet antibodies in platelet destruction and maintaining thrombocytopenia isn't negligible. As an example, a group of infants less than or equal to 2 years of age may present with "severe refractory thrombocytopenia," probably due to antiplatelet autoantibody. Moreover, disruptions in platelet function as well as remarkable and may give rise to bleeding and diminished platelet survival. WASp plays a key role in the process of platelet formation, activation, and associated cytoskeletal remodeling so that failure in platelet production and function is attributed to it. Increased expression of phosphatidylserine on the surface of circulating platelets has been interpreted as a sign of increased phagocytosis and destruction of platelets within the spleen in WAS/XLT. Whereas, decreased platelet production resulting from ineffective thrombocytopoiesis [6–8].

4.3 Immunodeficiency

Abnormalities in immune system function (i.e., cell-mediated, humoral, and innate immunity) among patients with WAS give rise to vulnerability to a wide range of infections pathogens. Nevertheless, infectious complications as a primary manifestation are not frequent (<5% of cases). Opportunistic infections such as molluscum contagiosum infections, extensive candidiasis, aspergillosis, and

Pneumocystis jirovecii may also present in WAS patients [5, 9, 10]. Patients with WAS can suffer from severe and disseminated forms of herpes simplex virus I or II (6% of cases) and varicella (3% of cases) as the most widespread pathogens. In 10% of cases, Invasive yeast and fungal infections have been reported. Generally, Sinopulmonary infections are classified as the most common infectious manifestation before diagnosis, including otitis media (64% of cases) and pneumonia. Other severe infectious complications are less likely to occur, such as sepsis (7% of cases) and meningitis (4% of cases) [6]. However, Viral infections caused by pathogens such as EBV, CMV, and HPV can be extremely severe.

In WAS patients, both quantitative and qualitative defects in T cells are manifested T cell lymphopenia as a common disorder is seen more in naive T lymphocytes than in memory cells and CD8. This event may result from increased apoptosis and can appear from early life and subsequently affect thymic output [11, 12]. More often than not, WAS patients have got an absolute lymphocyte count >1,000/μL, demonstrating the lack of the profound lymphopenia seen in other primary immunodeficiency disorders. Of note, an absolute lymphocyte count of <1,000/μL was presented in only 22% of cases. Processes such as T-cell activation, chemotaxis, and cytokine secretion are disturbed in patients with WAS [13, 14].

Humoral immunodeficiency is another characteristic of WAS patients. High serum levels of IgE and Low levels of IgM, IgG, and IgA are observed [5]. Abnormal isohemagglutinin titers (84% of cases) and insufficient vaccine responses to protein (e.g., 62% with abnormal responses to tetanus vaccine), polysaccharide (e.g., 69% with abnormal responses to the pneumococcal vaccine), and conjugate vaccines (e.g., 66% with abnormal responses to Hib (*Haemophilus influenzae* type b) conjugate vaccines, implies that antibody responses may be abnormal [5]. Malfunctions in T-cell mentioned earlier may disturb the maturation and differentiation of B cells into antibody-producing cells and memory cells [15].

Perturbations in the components of the innate immune response may also be present. The number of Natural Killer (NK) cells can be in the normal range or increase. Nonetheless, most of the time, NK cell function is abnormal, including Immunological synapse formation, stimulation of secretory granules, and consequent cytolytic activity [16]. Despite the normal numbers of neutrophils, monocytes, and other phagocytes, functional abnormalities may be present in WAS patients. Chemotaxis, adhesion/arrest function, DC motility, the initiation of degranulation, the formation of a functional respiratory burst, and antibody-mediated phagocytosis are more likely to be impaired [17, 18].

4.4 Eczema

Eczema is one of the specific findings that essentially leads to the differentiation of WAS from ITP. Skin manifestations resemble acute or chronic eczema in appearance and distribution. Eczema of varying severity occurs in approximately 50% of WAS patients during the first year of life and resembles classic atopic dermatitis. [2]. According to a large cohort study, 81% of WAS patients are classified into mild or severe, transient, or consistent, depending on their eczema history. In severe form, eczema resists therapy and lasts into adulthood. Based on some statistical evidence, Patients with XLT either have mild transient eczema or do not have any of these symptoms. It has been hypothesized that defects in the chemotaxis of DC and Langerhans cells, which are responsible for presenting specific (probably bacterial) antigens to T lymphocytes, cause eczema. Eczema is more complex in families with a history of atopic disease because the findings suggest that genes involved in allergic processes may have a modulatory effect [19, 20].

4.5 Autoimmune manifestations

According to collected data, autoimmunity is a frequent occurrence in patients with WAS. Reports indicate that 40% of patients with WAS develop autoimmunity and that many patients show various forms of autoimmune disease. A study affirms that Two-thirds of WAS patients who show autoimmune manifestations develop multiple autoimmune disorders. Autoimmune hemolytic anemia (14%), vasculitis (13%), renal disease (12%), and chronic arthritis (10%) are the most common manifestations of autoimmunity in WAS [5]. Autoimmunity in WAS may be due to the formation of autoantibodies or the presence of autoreactive T cell clones. Moreover, disorders in the homeostasis of regulatory T cells and B lymphocytes can lead to autoimmune disorders in WAS patients. Generally, the incidence of autoimmune disease is lower XLT than in classic WAS. A broad spectrum of autoantibodies has been detected both in classic WAS and in XLT. For example, high serum IgM levels are a risk factor for the development of autoimmune disease and early death [21, 22].

4.6 Malignancies

Malignancies can occur during childhood, whereas it is most likely to appear in adolescents and young adults with the classic WAS phenotype. B cell lymphoma (often Epstein-Barr virus-positive), leukemia, myelodysplasia, and myeloproliferative disorders are among the most frequent malignancies [6, 23]. Based on a cohort study, 13% of patients with WAS developed malignancy at a mean age of 9.5 years, and only 1 of 21 patients who developed a malignancy was alive more than two years after diagnosis [5]. The incidence of malignancies in patients with XLT phenotype is ambiguous and less than in classic WAS. In WAS patients, the prevalence of non-Hodgkin lymphoma (NHL) is more common than Hodgkin lymphoma (HL) [23]. Several NHL, such as Burkitt lymphoma and lymphoblastic lymphoma, have been reported rarely among patients with WAS. The aggressive nature of malignancy in the WAS patients represents a poor prognosis, as data demonstrate 95% mortality among patients. It should be noted that genetic susceptibility due to malfunction of WASp, associated abnormalities in tumor-surveillance mechanisms (e.g., impairment in NK cell cytotoxicity), and environmental factors (e.g., Epstein–Barr virus [EBV]) are significant components that increase the risk of malignancy in patients with WAS [24].

4.7 X-linked thrombocytopenia and X-linked neutropenia

XLT is assumed as congenital thrombocytopenia that is sometimes intermittent (IXLT). In such cases, the eczema is usually mild. Generally, XLT patients have got a benign disease as well as excellent survival in contrast to patients with WAS. serious hemorrhage in 13.9%, life-threatening infections in 6.9%, autoimmunity in 12.1%, and malignancy in 5.2% of XLT patients at median ages of 4.9 years, 24.8 years, 12.2 years, and 34.0 years, respectively. Every male with thrombocytopenia and small platelets should be evaluated for WASp expression and WAS gene mutations [25].

XLN presents mainly as a congenital and severe form of neutropenia. Unlike WAS, infectious complications due to T-cell immunodeficiency are absent. Impairments in immune function are similar to those explained for WAS. Nevertheless, Decreased NK cell count is a valid finding in XLN patients. Also, a slight decrease in platelet count has been reported. The potential risk of myelodysplastic syndrome and chronic myelocytic leukemia exists, which needs regular surveillance [26].

5. Histopathology

Gradually, the cellular elements in the thymus and lymphatic organs begin to disappear [27]. Depletion of small lymphocytes from T cell areas, reticular cell stroma protrusions, and the presence of abnormal plasma cells, often associated with extracellular plasmacytosis and hematopoiesis, are consistently seen in the lymph nodes and spleen of patients with WAS [28]. In a study of spleens obtained from WAS patients undergoing splenectomy, gradual depletion of the marginal zone involving B cells was also observed [29]. It may be possible to justify the disruption of the antibody response to selected polysaccharides and protein antigens by examining these histological abnormalities.

6. Diagnosis

WAS is an X-linked disease presented in males, with a lack of clinical symptoms in female carriers. Also, a deleterious mutation of the paternally derived X chromosome and inactivation of the maternally derived X chromosome lead to WAS in females, which is rare [30]. The diagnosis of WAS should be conducted in any male appearing with thrombocytopenia, eczema, recurrent respiratory infections, autoimmunity, etc (**Table 2**). Clinical findings may or may not be present during the course of the disease. Therefore, Because of evolution in clinical, physical, and laboratory findings, there is a dire need for Reassessment over time [5].

Physical exams	
Rash	Eczema
Bleeding	Petechiae, ecchymoses
Past medical history	
Rash	Eczema
Bleeding	Mucosal bleeding (easy bruising, epistaxis, hematochezia, hematuria) or intracranial hemorrhage
Infections	Recurrent or severe sinopulmonary infections, viral infections, fungal infections, or opportunistic infections
Autoimmunity	Cytopenias, vasculitis, inflammatory bowel disease, arthritis, renal disease
Malignancy	Lymphoma
Family history	
X-linked disorder	Every generation affected; predominant male susceptibility
Laboratory exam	
Complete blood cell count	Anemia, microcytosis, thrombocytopenia, low mean platelet volume
Peripheral blood smear	Microthrombocytes
Serum IgG, IgA, IgM, and IgE	Low lgG, lgA, lgM; high lgE
Isohemagglutinin and vaccine titers	Abnormal isohemagglutinin titers and diminished vaccine responses to protein, polysaccharide, and conjugate vaccines
Lymphocyte subsets and mitogen responses	T-cell lymphopenia and abnormal proliferative responses to mitogens

Abbreviation: Ig, immunoglobulin.

Table 2.
Clues to diagnosis of Wiskott–Aldrich syndrome [acc.6].

Despite the broad spectrum of clinical features, there is a considerable association between genotype and phenotype [9]. Mutations give rise to absent WASp expression and residual WASp expression are related to classic syndrome and XLT phenotype respectively. Also, gain-of-function mutations in the WAS gene result in XLN [31].

Interestingly, the patient phenotype may undergo genetic reversion, a selective advantage that can produce hematopoietic cells with normal WASP expression [32]. Screening for WASP mutations can be accomplished by flow cytometry using a suitable anti-WASP antibody. With this method, patients with expression of mutated WASP are likely to be miss. However, scrutinizing Sequence analysis of the WASP gene is essential to establishing a final diagnosis. It is speculated that the combination of two methods may help to estimate the severity of the disease [7].

7. Prognosis

The prognosis of X-linked thrombocytopenia has got a favorable position with a life expectancy close to the normal population [25]. Whereas, Classic Wiskott Aldrich syndrome has a poor prognosis with decreased life expectancy, which can be attributed to recurrent infections, autoimmune disease, and malignancy. Hemorrhage is the main cause of death in these patients [5].

As soon as a diagnosis is confirmed, the patient should be monitored and evaluated in a center with expertise in the management of WAS. It is clear that Without appropriate care and intervention, morbidity and mortality will not be unexpected. In a retrospective research, it has been demonstrated 36% of patients with WAS experienced non-HSCT-associated deaths at a mean age of 8 years. Mainly, these deaths are caused by infection (44%), bleeding (23%), and malignancy (26%) [5].

Many centers that provide look after WAS patients have multifaceted approaches to the care of patients and affected members of family, including genetic counseling, psychosocial support services, and subspecialist support, like transplant immunology, hematology/oncology, communicable disease, and important care. Of note, with appropriate care and timely intervention, WAS patients have an interesting prognosis. As an example, long-term survival following the utilization of allogeneic HSCT is >80% [31].

8. Treatment

Basically, the treatment of Wiskott-Aldrich syndrome depends on supportive care which includes Broad-spectrum antibiotics for bacterial, fungal, or viral infections. Furthermore, platelet supplement, Topical steroids and prevent bleeding, are other treatments. However, a series of controversial treatment are as follows (**Table 3**).

8.1 Intravenous Immunoglobulin therapy

Intravenous immunoglobulin (IVIG) therapy in WAS and XLT patients with significant antibody deficiency has led to efficient results. IVIG should be administered at physiological doses to patients with recurrent infectious complications and low levels of immunoglobulin or abnormal antibody responses [6]. Because of the increasing catabolic rate observed in WAS patients, the dose is higher than other immunodeficiency diseases. Since these people are more likely to bleed, a Subcutaneous injection of the IVIG is recommended [33]. In the presence of autoimmune manifestations, at least intermittently, immunosuppressive therapy may be required.

Conventional treatments
Broad-spectrum antibiotics
platelet supplement
Topical steroids
Potential treatments
Intravenous immunoglobulin (IVIG)
Splenectomy
Eltrombopag
Immunosuppressive treatment
Hematopoietic cell transplantation (HCT)
Gene therapy

Table 3.
Therapeutic approaches in Wiskott-Aldrich syndrome.

8.2 Splenectomy

Splenectomy is used to slow down the process of thrombocytopenia and stop bleeding by increasing the number of circulating platelets. Patients undergoing splenectomy consume antibiotics for life also they are highly vulnerable to septicemia [2]. Splenectomy is not recommended for people who are going to have Hematopoietic cell transplantation (HCT) in the future because it increases the risk of significant infectious complications [6, 7].

8.3 Eltrombopag

It is an oral thrombopoietin receptor agonist approved for the treatment of ITP which is claimed to probably effective in preventing bleeding in patients with WAS waiting for HCT [34].

8.4 Immunosuppressive treatment

More often than not, prescribing immunosuppressive drugs (e.g., cyclophosphamide, azathioprine) is necessary for the autoimmune phenomenon [35]. Most of the time, Monoclonal antibody rituximab may be effective in cytopenias due to Autoimmune disorders and it should be noted that the aforementioned antibody partly is harmless for patients already receiving therapy with IVIG [2].

8.5 Hematopoietic cell transplantation (HCT)

In a way, it can be said HCT is a unique treatment for patients with human leukocyte antigen (HLA)-matched family or unrelated donors (URDs) or relatively matched cord-blood donors [2].

Newly, according to haploidentical donors, novel graft manipulation approaches that alleviate the risk of graft versus host disease (GVHD) and elevate the possibility of successful engraftment, as well as immune system reconstruction, have yielded promising results in patients with WAS [36]. Reports indicate that The older you are at the time of transplantation, the lower your chances of survival, with different studies indicating different thresholds (e.g., age < 2 or < 5 years) [37, 38].

Despite the high chance of survival after transplantation for WASP patients, these patients are still at risk for post-HCT complications, among which autoimmunity is a prominent problem. It has been reported that up to 55% of transplanted WAS subjects develop autoimmune manifestations, mostly involving antibody-mediated cytopenias [39–42]. Although the risk of death in HCT is inevitable, according to a pervasive theory, patients with the severe phenotype (clinical score 3 and above) should be transplanted. For WAS patients with milder clinical manifestations, there is no unanimous opinion, and the decision to continue HCT is made on a case-by-case basis. The results of the decision-making process were the result of a retrospective study of the outcome of HCT in a group of 24 milder patients between 1990 and 2011 who were transplanted at various centers around the world. This study indicated a survival rate of 83% in the absence of long-term complications [43].

8.6 Gene therapy

Approximately, HCT from HLA-identical family donors is available to less than 20% of transplanted WAS patients [40, 43]. Although this approach is evolving [36], the increasing complications and mortality of HCT from mismatched donors [40] provide the idea for research into alternative kinds of gene therapy. Gene therapy prepares an enormous of potential advantages over allogeneic HCT, including availability for all patients, reduce transplant rejection risks and prevent GVHD risks, which successively eliminates the necessity to follow special diets and take immunosuppressive drugs. For the primary time in Germany, gene therapy for WAS was accomplished in a clinical trial, during which a gamma-retroviral vector was used to correct CD34+ cells from ten WAS patients. As a result of this investigation, nine of those individuals showed a significant increase in platelet count and rehabilitation of immune responses. But unfortunately, seven patients developed acute leukemia related to vector integration-mediated activation of the LMO2, MDS1, or MN1 genes [44, 45].

A High and unacceptable rate of cancer incidence in gamma-retroviral gene therapy paves the way for the implementation of clinical gene transfer protocols using HIV 1-based constructs [46]. Currently, a series of clinical trials in Europe and the U.S. using these lentiviral vectors have yielded encouraging preliminary results In 2010, when the primary trial was launched, Italian investigators have treated a minimum of 10 patients (F. Ferrua, personal communication, Barcelona, September 2016) with infusions of gene-corrected bone marrow and/or mobilized peripheral blood CD34+ hematopoietic cells. Then, they controlled the possible side effects by prescribing busulfan, fludarabine, and rituximab. The results of the first three patients ≥ 1 year after gene therapy indicated an improvement in platelet count and immune cell function additionally a reduction in severe infections and an improvement in eczema [47, 48]. The results of studies on the effect of gene therapy on defective B cells in patients with WAS indicate that standard distribution of bone marrow and peripheral blood cell subsets, in treated patients, is achievable. most significantly, a serious decrease within the abundance of naive B cells producing reactive antibodies, which are involved in improving the quantity of circulating antibodies altogether treated patients, was observed [49, 50].

The second investigation, conducted in London and Paris, using the identical lentiviral vector and a uniform reparative chemotherapy regimen, 6 out of seven patients treated also demonstrated improvement of immune function and clinical manifestations during 6–42 months of follow-up. Furthermore, during this study, no vector-mediated clonal expansions have occurred [51]. Of note, although in both

trials the duration of bleeding was significantly reduced in number and severity, and also the treated patients not needed blood transfusions and thrombopoietin receptor agonists, platelet counts failed to normal in either trial that it isn't clear. The third trial of WAS gene therapy supported lentiviral vector has recently begun in Boston, USA [52]. At the identical time, other US researchers have developed an alternate lentiviral vector with a stronger WASp expression that's being developed for future clinical applications [53, 54].

In line with current studies, it will be acknowledged that gene modification by lentivirus from autologous hematopoietic ancestors can have significant benefits for patients undergoing treatment and be considered as treatment options for WAS. However, more comprehensive studies are needed to ascertain whether this type of gene therapy could also be a definitive treatment for patients.

9. Conclusions

Despite the rarity of WAS, extensive progress has been made in understanding its pathophysiological foundations, but it is still necessary to establish multifaceted management to assess various aspects of the disease. It is worth noting that health care centers have been pioneers in the diagnosis and management of WAS. Significant advances in allogeneic HCT and its valuable long-term results have made it a viable treatment option for most patients with WAS. For severe manifestations, for example, definitive treatment with HCT is recommended. However, even in a clear clinical situation, HCT may not be available due to the patient's geographical location or socioeconomic status, so supportive care measures should be taken promptly. The same is true of WAS cases with milder clinical manifestations; In fact, more emphasis is placed on accepting the potential risks of treatment in proportion to the severity of the disease manifestations.

Gene therapy is a potential treatment solution for WAS patients with severe and even mild phenotypes. In this regard, the emergence of advances in the use of gene editing technology creates a cautious optimism. However, the financial and geographical problems for patients with limited access to gene therapy options need to be addressed.

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Conflict of interest

The authors declare no conflict of interest.

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Abbreviations used

HCT	Hematopoietic stem Cell
ITP	Idiopathic thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
WAS	Wiskott-Aldrich syndrome
WASp	Wiskott-Aldrich syndrome protein
XLT	X-linked thrombocytopenia
XLN	X-linked neutropenia

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