Editorial

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Mavorixafor, CXCR4 antagonist, a novel treatment for WHIM syndrome, first FDA approval 2024

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Abstract

Warts, Hypogammaglobulinemia, recurrent bacterial Infections, and Myelokathexis syndrome is a rare autosomal dominant disorder characterized by gain-of-function mutations in chemokine receptor type-4 (CXCR4 receptor). The acronym WHIM stands for Warts, Hypogammaglobulinemia, recurrent bacterial Infections, and Myelokathexis. Traditionally, WHIM syndrome has been managed with intravenous immunoglobulin (IVIG) and filgrastim (granulocyte colony-stimulating factor). Intravenous immunoglobulin is used to provide passive immunity to counteract hypogammaglobulinemia, while filgrastim stimulates the production and release of neutrophils from the bone marrow to address neutropenia. However, these treatments have limited efficacy, require frequent administration, and involve significant costs and patient burden. The recent Food and Drug Administration (FDA) approval of Mavorixafor, a small-molecule CXCR4 antagonist, marks a significant advancement in the management of WHIM syndrome. Mavorixafor enhances white blood cell mobilization from the bone marrow, directly targeting the underlying cause of the disease. In a pivotal phase-3 trial conducted by Badalato *et al*, involving 30 participants randomized to receive Mavorixafor 400 mg daily or placebo for 52 weeks, Mavorixafor demonstrated a statistically significant increase in absolute neutrophil count ($P < 0.01$) and a notable reduction in annual infection frequency compared to placebo. Additionally, a Phase-2 study reported a 75% reduction in cutaneous warts and an annual infection rate of 2.27 occurrences with adequate dosing. Mavorixafor maintained a favorable safety profile and required fewer administration complexities than IVIG and filgrastim, with 78% of patients achieving an overall response compared to 10% in the placebo group. These findings underscore the potential of Mavorixafor to significantly improve clinical outcomes for patients with WHIM syndrome, offering a more effective and targeted treatment option. The approval of Mavorixafor not only enhances current therapeutic strategies but also paves the way for future research into CXCR4 antagonists, potentially revolutionizing the management of WHIM syndrome and similar immunodeficiencies.

To the Editor,

Warts, Hypogammaglobulinemia, recurrent bacterial Infections, and Myelokathexis (WHIM) syndrome is an autosomal dominant disorder caused by gain-of-function mutations in the chemokine receptor type-4 (CXCR4). WHIM is an acronym for its significant features: Warts, Hypogammaglobulinemia, recurrent bacterial Infections, and Myelokathexis (apoptosis of mature myeloid cells in the marrow)[1,2]. In 1964, Wolf Zuelzer from the Wayne State University School of Medicine and Krill and his associates from the University of Cincinnati were the first to report a severe congenital neutropenia known as Myelokathexis. They uncovered myelokathexis due to the recent bacterial infection found 6 weeks apart in a 9-year-old[3,4]. According to Walter and Ballow (2019), WHIM syndrome has been documented in only 109 cases worldwide, highlighting its rarity and diagnostic challenges[5].

In childhood, individuals suffering from WHIM syndrome manifest with recurrent bacterial infections, including sinusitis, ear infections, and pneumonia. Hearing loss and bronchiectasis can develop due to ear infections, but growth and development remain normal. Other infections include meningitis, gum infection, cellulitis, thrombophlebitis, and omphalitis. Most of these infections include viral infections, which present with benign course, unlike other immunodeficiency syndromes where it can lead to significant threats. Warts are the most common manifestation caused by the human papillomavirus virus. They are found commonly on the dorsal surface of the hand but can occur in the genital mucosa and skin[6].

A confirmed diagnosis requires CXCR4 gene sequencing, which typically reveals one of the hallmark mutations affecting the CXCR4 intracellular tail. Most of the mutations are nonsense, resulting in a premature stop codon that truncates the receptor's cytoplasmic C-terminus tail. The mutation R334X (CXCR-4 gene mutation) was detected in 24 patients, but the others were found in only 1–4 cases. Approximately one-third of WHIM cases are sporadic, with the majority following an autosomal dominant inheritance pattern, complicating prenatal diagnosis if one parent is affected. Umbilical cord blood cells can be used for genetic analysis and

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validated with peripheral blood samples. Some patients with WHIM clinical characteristics do not have CXCR4 mutations[6].

Individuals with WHIM syndrome are characterized by a severe reduction in B cells, while there is less reduction in T cells and monocytes and hence panleukopenia[7]. White blood cells are released from the bone marrow into the blood under the control of CXCR4 and its ligand motif chemokine ligand-12 (CXCL12). WHIM syndrome manifests with increased signaling of CXCR4 and its ligand, which leads to the retention of mature apoptotic neutrophils inside the bone marrow, and then it presents clinically with neutropenia with or without monocytopenia and lymphopenia[8]. Currently, WHIM syndrome is treated by IVIG and filgrastim (granulocyte colony-stimulating factor). They have limited efficacy, are complex to administer, and are expensive[9]. Plerixafor, a small-molecule competitive inhibitor of CXCR4, is a potent hematopoietic stem cell mobilizing agent in cancer and has been approved for short-term use by the US FDA[7]. Fine-tuning the long-term dosing of antagonists is of high importance, as a complete block of CXCR4 signaling can be harmful, as shown in human immunodeficiency virus patient studies[5].

Before the introduction of Mavorixafor, individuals with WHIM syndrome faced considerable hurdles due to the limited efficacy and burdensome administration of therapies such as IVIG and filgrastim. Despite these interventions, recurring infections and severe neutropenia remained common, underlining the critical need for more effective targeted therapies. Historically, the management of WHIM syndrome was complicated, with medicines providing only partial alleviation and no cure, emphasizing the significance of advances such as Mavorixafor.

Mavorixafor is a recent FDA-approved small-molecule CXCR4 antagonist for WHIM syndrome that enhances white blood cell mobilization. The approval was underpinned by key clinical trials, including a Phase-2 study and a pivotal Phase-3 trial. These trials employed rigorous randomized, double-blind, placebo-controlled methodologies, focusing on primary end points such as increased absolute neutrophil count (ANC), reduction in infection rates, and secondary safety end points. The study designs ensured a high level of evidence supporting Mavorixafor's efficacy and safety. In a Phase-2 study conducted by Dale *et al*, Mavorixafor demonstrated a 75% reduction in cutaneous warts and an annual infection rate of 2.27 occurrences with a daily dose of 400 mg. This study supports Mavorixafor's efficacy in mobilizing neutrophils and lymphocytes, suggesting potential long-term clinical benefits for patients with WHIM syndrome. Mavorixafor also inhibits Ca2+ mobilization and CXCL12-dependent extracellular signal-regulated kinase and protein kinase B (ERK/AKT) activation in cells with both wild-type and WHIM variant CXCR4. It effectively prevents CXCL12-induced hyperactivation of ERK and AKT across various CXCL12 concentrations.

The FDA-approved Mavorixafor following a Phase-3 trial conducted by Badalato *et al*, which was a randomized, double-blind, placebo-controlled investigation involving 31 individuals with genetically confirmed WHIM syndrome. In this trial, 14 participants received Mavorixafor 400 mg daily, and 17 participants received a placebo, over a period of 52 weeks. The primary outcome was the change in ANC from baseline, with secondary end points including the yearly infection rate and total white blood cell count. The research found a significant rise in ANC ($P< 0.01$) and a notable reduction in annual infection frequency in the Mavorixafor group compared to placebo, highlighting the drug's efficacy and safety profile. It is essential to note that while the frequency of infections was significantly reduced, the severity of infections was not addressed in the trial findings. Additionally, the study indicated no significant change in the number of warts.

Table 1 compares treatments for WHIM syndrome, highlighting Mavorixafor's efficacy and safety alongside other options.

The most frequently reported adverse reactions were thrombocytopenia (low platelet counts), rash, rhinitis (stuffy nose), epistaxis (nosebleed), vomiting, and dizziness. While these adverse effects were generally low to moderate in severity, their impact on long-term use and patient adherence should not be underestimated. The risk of cumulative toxicity, especially with prolonged usage, raises questions regarding the drug's long-term safety. The requirement for regular monitoring and the possibility of drug interactions, particularly in patients with comorbidities needing polypharmacy, may make adherence even more difficult. These variables emphasize the significance of designing complete management regimens that include patient education, continuous follow-up, and efforts to reduce adverse effects to optimize long-term outcomes and

Table 1

Comparison of mavorixafor with other treatments for WHIM syndrome.

Treatment	Study design	Year	Efficacy	Safety	Reference number
IVIG	Observational study	1990	Efficacy: Manages hypogammaglobulinemia; limited impact on neutropenia and other WHIM symptoms	Generally safe; potential for allergic reactions or infections	1
Plerixafor	Clinical trial	2011	Efficacy: Significant improvement in neutropenia and stem cell mobilization	Safety: Generally well-tolerated; side effects include nausea, fatigue, and injection site reactions	7
Mavorixafor	Phase 2 trial	2020	Efficacy: 65% reduction in infections; 55% improvement in neutrophil counts	Safety: Well-tolerated; common adverse effects include rash, headache, and diarrhea	10
	Phase 3 trial	2024	Efficacy: 70% improvement in neutrophil counts; 60% reduction in infections	Safety: Similar to Phase 2; additional adverse effects include thrombocytopenia	11
HSCT	Case study	2016	Efficacy: Can achieve long-term remission; outcomes vary based on engraftment success	High risk of complications including graft-versus-host disease and infection	12
Umbilical cord blood stem cell transplantation	Case Study	2010	Efficacy: Effective in children; outcomes similar to HSCT but may have a lower risk of some complications	Risks include graft-versus-host disease, infection, and procedural complications	13
Gene editing	Case study	2015	Efficacy: Promising in preclinical models; potential for long-term cure	Experimental; long-term safety data not yet available	15

IVIG, intravenous immunoglobulin; HSCT, hematopoietic stem cell transplantation.

adherence. It can cause fetal harm, so women of childbearing potential should be advised to use effective contraception[10]. Several studies have shown that hematopoietic stem cell transplantation (HSCT) can effectively treat WHIM syndrome[11-13]. After a chromothripsis deletion in one patient, the spontaneous mutation led to a cure for WHIM syndrome, demonstrating the potential of gene editing as a therapeutic approach[14]. However, a few constraints must be considered when interpreting these findings. For example, the Phase-3 trial's relatively small sample size of 31 patients may limit the findings' applicability to a larger population. Furthermore, while the study's duration was sufficient to demonstrate short-term efficacy and safety, it may not have captured long-term outcomes and possible danger associated with chronic Mavorixafor usage. Future research with bigger, more diverse cohorts and longer follow-up periods is required to confirm these findings and assure their generalizability to a larger patient population.

In conclusion, there has been a rise in recognition of WHIM syndrome cases in recent years. Mavorixafor offers hope to individuals and medical professionals struggling to manage WHIM syndrome. Its ability to reinvent treatment regimens demonstrates the hope and possibilities that innovative medicines might bring to genetic medicine. To fully realize Mavorixafor's potential, immediate action is needed in research and clinical practice. We urge continued investigation into its long-term safety and efficacy, as well as studies exploring its use in combination with other therapies. Additionally, the potential of CXCR4 antagonists extends beyond WHIM syndrome. This includes exploring their potential efficacy in certain cancers where CXCR4 signaling contributes to tumor progression and metastasis, as well as in autoimmune disorders where modulation of immune cell trafficking may offer therapeutic benefits. Ongoing clinical trials and post-marketing surveillance are essential for refining treatment strategies and addressing any emerging concerns.

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