Evolving role of the interleukin-5 antagonist mepolizumab for hypereosinophilic syndrome: pathogenesis and advances in therapy - A narrative review

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ABSTRACT

Hypereosinophilic syndrome (HES) is a rare blood disorder characterized by hypereosinophilia greater than 1,500/μL on at least two separate occasions with some degree of associated end-organ damage and exclusion of other identifiable causes of hypereosinophilia. The systemic effects and damage seen in HES can be extensive, resulting in a variety of clinical presentations, but most commonly the affected organs include the lungs, heart, skin, and the gastrointestinal tract. After FDA-approval in 2020, mepolizumab (trade name Nucala) an interleukin-5 (IL-5) antagonist monoclonal antibody, is considered an effective treatment for HES given its ability to lower absolute eosinophil counts, improve the symptomatic burden, reduce the number of HES flares experienced, and limit the need for corticosteroids as a primary therapy. Also of benefit, Nucala has been shown to have a positive safety profile with limited adverse effects and no notable contraindications to treatment.

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Introduction

Hypereosinophilic syndrome (HES) is a broad diagnosis encompassing pathologies of varying etiology. It is considered a rare blood disorder characterized by two distinct criteria, the first of which is persistent eosinophilia with an elevated absolute eosinophil count (AEC) greater than 1,500/μL on at least two separate occasions. The second criterion is identified end-organ damage.[1,2] While there remains some debate over the categorization of eosinophil-derived disorders, a more recently proposed classification system divides hypereosinophilia (HE) into either a primary, secondary, or idiopathic etiology, with HES being diagnosed once end-organ damage is present and no other identifiable cause can be deduced.[2] This damage is not restricted to any one area of the body, and while some patients have extensive symptomatic profiles, the most commonly affected organs of eosinophil-induced damage include the gastrointestinal tract, lungs, heart, and skin.[1] Tissue infiltration by persistently elevated eosinophil levels causes the release of eosinophil-derived mediators and cytotoxic proteins that cause organ system damage, thus contributing to the pathogenesis of HES.[2] While glucocorticoids and other immunomodulatory agents remain first-line agents for the treatment of HES, monoclonal antibody therapy has been explored and more recently approved by the Food and Drug Administration (FDA) as a treatment option.[3] These treatment options include mepolizumab, an interleukin-5 (IL-5) antagonist that goes by the brand name Nucala. In addition to Nucala's approval for use in HES in 2020, the drug is also indicated for severe asthma with an eosinophilic phenotype, chronic rhinosinusitis with nasal polyps (CRSwNP), and

eosinophilic granulomatosis with polyangiitis (EGPA).[4] By antagonizing the IL-5 receptor, Nucala blocks the normal physiologic function of IL-5, which typically acts as the major cytokine involved in eosinophils' proliferation, activation, and survival.[3] Due to this effect, it is proposed to have therapeutic benefits in a wide array of eosinophilic disorders.

In order to meet the criteria for HES treatment with Nucala, patients must be twelve years or older and have had HES for at least six months without an identifiable non-hematologic secondary cause.[4] Nucala has demonstrated limited adverse reactions in patients with no notable contraindications to therapy following administration by injection, illustrating a positive patient safety profile. The most common adverse effects reported include headache, injection site reaction, back pain, and fatigue.[4] Before drug approval, clinical trials consistently showed Nucala's utility in lowering AEC counts to <600/μL (normal levels are 500/μL or less) for at least eight consecutive weeks, as well as the drug's efficacy in reducing the oral intake of steroids needed by patients.[5,6] Additionally, one randomized, double-blind, multicenter, placebo-controlled trial including 108 patients with HES showed that Nucala is useful in limiting the number of HES flares experienced by patients while demonstrating statistically significant improvements in breathing symptoms, abdominal pain and muscle/joint pain.[7,8] Overall, this therapy has been shown to be very effective in impacting disease progression in HES and to positively influence patients' quality of life without a significant burden of side effects.

Clinical presentation and diagnosis of HES

HES is a broad term that unifies multiple eosinophil-derived disorders that have progressed to include end-organ damage in addition to HE as sequela while not meeting criteria for other diagnoses. Peripheral blood eosinophilia can be defined by either a relative blood eosinophilia when eosinophils account for >6% in differential counts or an absolute blood eosinophilia (ABE). ABE can be further divided into mild eosinophilia ranging from 500-1,499/μL, moderate HE, ranging from 1,500-5,000/μL, and severe HE, when eosinophil count is greater than 5000/μL.[2] HE can be further partitioned into primary, secondary, or idiopathic etiologies, with primary forms normally being neoplastic in nature and secondary HE encompassing more reactive etiologies, including infection or inflammation that respond to IL-5 producing cells.[1] Treatable conditions that are often characterized by high eosinophil count include parasitic infections, allergic disease, some cancers, drug reactions, and autoimmune diseases. It is important that these other causes for high eosinophil count be excluded before HES can be formally diagnosed, given that HES is foremost a diagnosis of exclusion.

HES is classified into several diagnostic subtypes: myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion, chronic eosinophilic leukemia (CEL), lymphocyte-variant hypereosinophilia (L-HES), and idiopathic HES.[9] These subtypes are differentiated by their underlying mechanism of eosinophil overproduction; this can include a clonal (neoplastic process), a reactive cause such as infection or autoimmunity, a mixed mechanism as seen in L-HES, or remain idiopathic.[9] The diagnosis for HES is based on exclusion other conditions. The exclusion process usually involves: first, ruling out secondary/reactive causes (e.g., infection, autoimmune, drug reactions), then assessing for clonal or neoplastic disorders, and, last, evaluating for aberrant T-cell populations consistent with L-HES. If no identifiable cause is determined, a diagnosis of idiopathic HES is made.[9] Common manifestations of HES include fatigue, cough, shortness of breath, myalgias, rash, angioedema, rhinitis, and fever. Although, HES presents with a wide range of symptoms, eosinophil-mediated organ damage remains the most serious complication- including cardiac involvement that may progress to restrictive cardiomyopathy or valvular dysfunction.[9]

In terms of defining eosinophil levels in HES, AEC must at least meet moderate HE standards (AEC >1,500/μL).[7] Depending on the organs affected, HES can present non-specifically with various systemic symptoms, so clinical presentation can be extremely variable. If HES is expected, a thorough evaluation of the extent of effector organ damage is vital for the prevention of disease morbidity and mortality. Referral to an allergist or immunologist is often necessary during the diagnostic phase, with further testing geared towards ruling out other treatable causes of eosinophilia. After the diagnosis of HES, a chest X-ray, and echocardiogram are utilized to evaluate any degree of organ damage that may be present in both the heart and lungs, given these are two of the most commonly affected organs.[2] Historically HES treatment has been targeted at reducing eosinophil levels in order to minimize end organ damage, particularly within the heart. Common treatments include corticosteroids, hydroxyurea, chlorambucil, vincristine, methotrexate, and, more recently, monoclonal antibody therapy, including treatment with Nucala.[8,10] Prognosis is variable and dependent on the degree of disease severity at diagnosis; however, due to improving treatment options, survival has grown to a five-year survival rate of 80% *vs* a previous three-year survival rate of 12% in the 1970s.[11] Overall, on making the diagnosis of HES, any patient with defined HE with evidence of end-organ damage supported by imaging and laboratory tests, and who has failed to meet criteria for another distinguished condition, can be formally identified as having HES.

Nucala mechanism of action, safety and tolerability

Mepolizumab, a fully humanized monoclonal antibody, acts as IL-5 antagonist. IL-5 has a vast scope of function, including being the primary driver of eosinophils differentiation and function. Mepolizumab competitively binds the α-chain of the eosinophil cell surface receptor complex blocking binding to IL-5 thus inhibiting signaling from the latter. It reduces eosinophil growth, differentiation, mobilization, recruitment, activation, and survival. In addition to IL-5, IL-3 and granulocyte-macrophage colony-stimulating factors are chief signaling factors in the development of basophils and eosinophils, with IL-5 being more selective for eosinophils and IL-3 being more selective for basophils. However, activation of IL-5 receptors is not a prerequisite for basophils to fulfill their functional roles. Consequently, eosinophil-driven pathology such as asthma, atopic dermatitis, EGPA, eosinophilic esophagitis/gastroenteritis, and HES are primarily mediated by IL-5.[1,7,12-15] The safety and tolerability of mepolizumab have been assessed through numerous clinical trials, revealing various adverse effects (AEs), hypersensitivity reactions, and considerations regarding its use. Regarding hypersensitivity reactions, mepolizumab may cause anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, and rash.[13-16] However, the overall incidence of sys-

temic hypersensitivity reaction is rare. In one study, incidence was 1% in the mepolizumab group *vs* 2% in the placebo group.[16]

Common AE's of mepolizumab experienced in the GSK clinical trials included headache (19%), injection site reactions (8%), back pain (5%), fatigue (5%), and influenza (3%).[16] Mepolizumab was generally well-tolerated in other trials, with similar proportions of patients experiencing AEs in the mepolizumab group (89%) and the placebo group (87%).[7] Drug-related AEs were reported more frequently in the mepolizumab group (22%) than in the placebo group (13%).[7] Frequently reported AEs were bronchitis, diarrhea, headache, nasopharyngitis, pain in the extremities, pruritus, rhinitis, and upper respiratory tract infection with only URI's being notably more prevalent in the on-treatment group (4% *vs* 15%).[7] In another study with subjects who had HES, 65% experienced an AE, with diarrhea, pruritus, and headache being the most common, but only 15% were related to mepolizumab.[15] Serious AEs occurred in 9%, with one event (sinusitis) related to the study treatment. Additionally, 35% of patients experienced infections/infestations, which was the most common on-treatment AE.[14] In one study, 4% of patients treated with mepolizumab tested positive for anti-mepolizumab antibodies, leading to no serious AE's.[12]

In children, mepolizumab appears to be safe and well-tolerated. In the open-label study by Gupta, no children experienced serious AEs, and on treatment AE's due to mepolizumab were only found in about 24% of children.[13] The most common of these symptoms were headache, upper abdominal pain, and fever; 73% of children contracted an infection while on treatment but that was not determined to be drug related.[13] Although no drug-related events leading to treatment discontinuation were noted throughout this review, it is essential that mepolizumab not be discontinued abruptly in patients taking corticosteroids. Abrupt discontinuation may lead to systemic withdrawal symptoms previously suppressed by corticosteroid therapy.[16]

Indications

Mepolizumab, a monoclonal antibody that targets interleukin-5, has emerged as a pivotal therapeutic agent in the management of several eosinophil-driven disorders.[15-18] Mepolizumab demonstrated clinical efficacy in various scenarios, highlighting its potential for further indications. Mepolizumab's role as an add-on maintenance treatment has been affirmed in severe eosinophilic asthma in adult and pediatric cases aged six years and older.[15] Mepolizumab has demonstrated an ability to reduce asthma exacerbation rates, improve lung function, and enhance the quality of life for these patients.[14,15] A study provides compelling evidence for this role, revealing significant reductions in asthma exacerbation rates in patients enduring recurrent asthma exacerbations and eosinophilic inflammation despite high dose inhaled glucocorticoid use. Mepolizumab reduced exacerbation rates compared to placebo by 47% and 53%, respectively.[13] The study conducted by Bettiol *et al.* further substantiates this theory by showcasing a significant reduction in oral glucocorticoid dosage, a decrease in annual asthma exacerbation rate, improvement in quality of life and lung function measures with mepolizumab treatment in severe asthma.[19] Importantly, mepolizumab is not recommended for acute bronchospasm or status asthmaticus, underscoring its function as a maintenance therapy in chronic conditions.[4,16] Furthermore, in adults with chronic rhinosinusitis and nasal polyps who have not responded sufficiently to corticosteroids, mepolizumab provides additional benefit.[16]

Similarly, mepolizumab shows therapeutic promise[1,13,17,18] and in the recent phase 3 clinical study by Bettiol *et al.* which highlighted the efficacy of mepolizumab as a treatment modality for eosinophilic granulomatosis with polyangiitis.[19] This trial demonstrated that mepolizumab was more effective than the placebo in terms of increasing the number of remission weeks (28% of mepolizumab recipients had 24 or more remission weeks compared to 3% in the placebo group; odds ratio, 5.91; $p<0.001$).[20] The proportion of cases achieving remission at both the 36 and 48-week marks was notably higher in the mepolizumab group (32% *vs* 3%; odds ratio, 16.74; $p<0.001$).[16] Mepolizumab was also associated with a significantly reduced annual relapse rate (1.14 compared to 2.27 in the placebo group; rate ratio, 0.50; $p<0.001$).[16] Additionally, mepolizumab enabled a substantial decrease in the daily glucocorticoid dose during weeks 48 to 52, with 44% of patients requiring 4.0 mg or less daily, in stark contrast to the 7% in the placebo group (odds ratio, 0.20; $p<0.001$).[19]

In HES, mepolizumab has shown effectiveness in adults as well as pediatric patients (12 years+) with persistent eosinophilia for 6 or more months and lacking a non-hematologic secondary cause.[1,12,15] Moreover, recent trials have reported mepolizumab's efficacy in controlling eosinophils. and demonstrating a steroid-sparing effect in adults with FIP1L1-PDGFRA fusion gene negative HES and lymphocytic variant HES.[15] Notably, it was well-tolerated over long-term use with few serious side effects. Case studies involving pediatric patients and individuals with idiopathic HES have also highlighted mepolizumab's potential efficacy.[15,18]

Collectively, these findings point towards an expanded role for mepolizumab in managing eosinophilic conditions while also underscoring the need for further investigation into additional therapeutic indications.

Long term benefits/goals of therapy

There are multiple etiologies for HES, but the defining feature of end-organ damage requires quick and effective workup and treatment.[1] The most commonly affected organs such as the skin, lungs, and GI tract.[20] Neurologic and cardiac complications occur as well but less frequently.[20] Without treatment, the end organ damage caused by HES can lead to potential morbidity and mortality. Additionally, a large study showed that approximately 5.1% of patients with hypereosinophilia developed a hematologic malignancy, which occurred, on average, 30.0 months after the onset of hypereosinophilia.[21] Given this increased risk for malignancy, patients and their physicians can be more prepared for screening and treatment of malignancies based on the early recognition and treatment of HES.

The initial treatment is typically with glucocorticoids with the goal of reducing eosinophil count, but eventually, a more personalized, steroid-sparing therapy can be selected based off the specific subtype. Mepolizumab is a humanized anti-IL-5 antibody that studies have demonstrated to be efficacious in treating severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis.[1] Studies have also demonstrated the efficacy of mepolizumab for treating HES and reducing the need for steroids. In one study on mepolizumab, the median daily prednisone dose reduced from 20.0 to 0 mg in the first 24 weeks, with 62% of subjects were prednisone-free for greater than 12

weeks.[6] Another randomized control trial found that 84% of patients receiving mepolizumab and 43% receiving the placebo reduced the prednisone dose to less than or equal to 10 mg per day for more than 8 consecutive weeks during the 35-week treatment period,[5] which increases the impact on patient outcomes because the medication has a multifactorial approach as it reduces absolute eosinophil count and reduces the need for high dose steroids. Glucocorticoids have many well-known adverse effects, including hypertension, diabetes mellitus, and obesity.[22] These are all independent risk factors for cardiovascular disease. A more recent population study reported that patients exposed to more than 7.5 mg of prednisolone daily during one to five years had substantially higher rates of myocardial infarction, heart failure, and cerebrovascular disease. There was a higher rate of congestive cardiac failure in patients exposed to low dose glucocorticoids.[23] Long-term glucocorticoid treatment is also associated with musculoskeletal effects such as osteoporosis, osteonecrosis, and steroid myopathy. The treatment can also lead to peptic ulcers, pancreatitis, and fatty liver disease. There are also known behavioral side effects such as insomnia, emotional instability, and cognitive impairment.[24] Utilizing biologic therapies like mepolizumab to treat HES may reduce the need for long-term glucocorticoid treatment, which may improve patient outcomes.

Finally, HES flares are associated with significant morbidity, have a significant negative effect on patients' quality of life, and can be life threatening.[25] Flares often necessitate prolonged use of oral corticosteroids along with immunosuppressants or cytotoxic therapy.[9] As discussed above, these treatments have associated risks, so it is important to utilize a medication that reduces flares. Mepolizumab has been shown to have a 50% reduction in the proportion of cases experiencing at least one flare and a 66% reduction in the annualized flare rate *vs* placebo.[7] Additional analysis of this data demonstrated that mepolizumab also reduced the median duration of flares compared to placebo (Table 1).[26-28]

Discussion

At present, there is agreement that HES is a group of disorders characterized by prolonged blood eosinophilia and eosinophil related end-organ damage. This damage occurs *via* eosinophil release of cytotoxic chemicals, including eosinophil cationic protein, major basic protein, eosinophil peroxidase, free oxygen radicals, and enzymes like elastase and collagenase.[10] Eosinophils also affect vascular and bronchial smooth muscle tone *via* their production of leukotrienes and prostaglandins. Finally, eosinophils secrete pro-inflammatory cytokines and TGF-beta, leading to enhanced collagen synthesis and extracellular matrix deposition.[10] The complex interactions between eosinophils and the immune system and their ability to affect any tissue or organ lead to a variety of clinical manifestations. The symptoms range from cutaneous manifestations such as angioedema and urticarial lesions, cardiac involvement leading to cough, dyspnea or orthopnea, neurologic manifestations leading to diffuse encephalopathy or peripheral polyneuropathy, pulmonary manifestations like chronic dry cough or bronchial hyperreactivity, hematologic manifestations including anemia or thrombocytopenia, coagulation disorders, GI manifestations like abdominal pain, diarrhea, nausea, or vomiting, and constitutional symptoms like weakness, fatigue, anorexia, fever, and night sweats.[11] Given the severity of these life-threatening symptoms, it is vital to have effective and tolerable treatments for HES.

Conclusions

HES is typically treated with glucocorticoids as they are known to cause apoptosis of eosinophils.[9] However, the clinical response is variable depending on the HES subtype, on the other hand cardiovascular risk factors and other toxic side effect profiles are associated with long-term use of glucocorticoid therapy. There is emerging research on the use of mepolizumab for the treatment of HES. Mepolizumab is a targeted, humanized monoclonal antibody that selectively binds to IL-5.[7] It is currently approved for use in cases with severe eosinophilic asthma and eosinophilic granulomatosis. It works by binding to free IL-5 with high affinity and specificity, thus preventing IL-5 from interacting with receptor alpha chains on the surface of eosinophils and their progenitors.[5] This action functions to reduce the absolute eosinophil count, thereby reducing the end-organ damage and hopefully improving mortality and morbidity. Mepolizumab is also well tolerated as a randomized control trial demonstrated adverse events were reported at similar rates in both the placebo and experimental groups.[5] That same study demonstrated the efficacy of mepolizumab at significantly reducing blood eosinophil count and mean serum eosinophil-derived neurotoxin levels compared to placebo. Additionally, the study reported a significant reduction in the required dose of glucocorticoids in patients on mepolizumab therapy, thus protecting patients from some of the negative side effects like cardiovascular disease.[5,21] There is currently an ongoing, open-label extension trial that will help to provide long-term information on drug safety and optimal dosing frequency. There is still more to be discovered regarding mepolizumab's efficacy and safety profile, but initial clinical trials demonstrate a potential clinical benefit for those with HES.

Table 1. Clinical studies related to Nucala for hypereosinophilic syndrome.

Author (year)	Groups studied and intervention	Results and findings	Conclusions
Roufosse *et al.* (2020)[7]	Clinical Trial ID: 200622 • Patients with uncontrolled FIP1-like-1-platelet-derived growth factor receptor α-negative HES participated in a multi-center (39 centers in 13 countries), double-blind, placebo-controlled phase 3 clinical trial • Patients received 300 mg subcutaneous mepolizumab or placebo every 4 weeks for 32 weeks along with existing HES therapy	• 28% of mepolizumab treated patients experienced 1 or more flares *vs* 56% of placebo patients • A similar proportion of patients in experimental and placebo groups experienced adverse events (89% and 87%, respectively)	Mepolizumab treatment significantly reduced flares in *FIP1L1-PDGFRA*-negative HES patients compared to placebo and introduced no increased safety risk
GlaxoSmithKline (2022)[4]	• Open label phase 3 clinical trial with single study arm with pediatrics age 6-17 with HES Patients will receive mepolizumab subcutaneously for 52 weeks	• Primary outcome measured will be total number of HES flares during trial • Change in mean daily oral corticosteroid use • Number of participants who develop anti-drug antibodies • Changes in blood eosinophil count from baseline	Clinical trial is current
Pane *et al.* (2022)[25]	• *Post-hoc* analysis of above clinical trial (200622) trial to characterize disease flares	• Most common flare types were constitutional (94%), dermatological (82%), and respiratory (72%) • Median duration of flares was reduced by half in mepolizumab treated group *vs*. placebo	Mepolizumab is effective in reducing the number of HES flares
Gleich *et al.*, (2021)[26]	• Patients who participated in the above phase 3 clinical trial (200622) were given the option to join this open-label extension study • Patients received 300mg mepolizumab subcutaneously every 4 weeks for 20 weeks	• 65% of patients reported adverse events (AEs) • 15% reported treatment related AEs • 9% reported serious AEs • 28% of previously placebo patients receiving oral corticosteroids saw a ≥50% reduction in mean daily dose in weeks 16-20 • Previously placebo patients saw an 89% reduction in blood eosinophil count at week 20	This study reveals that subcutaneous mepolizumab can be used effectively in long term management of *FIP1L1-PDGFRA*-negative HES without increased safety risk
Roufosse *et al.* (2023)[27]	• Analysis of symptom burden during 200622 tria • l6 HES-related symptoms identified as most bothersome by patients were rated daily on a scale 1-10	• Mepolizumab significantly decreased patient HES daily symptom scores from baseline when compared to placebo at week 32 • Parametric analysis showed mepolizumab improved HES-DS scores after first dose and the changes were maintained over time • Mepolizumab treatment improved all individual categories of symptoms except skin symptoms (itchiness, rashes, hives) ○ All improvements were statistically significant compared with placebo except chills/sweats	Mepolizumab treatment displays promising potential in reducing a variety of bothersome symptoms of HES
Roufosse *et al.* (2010)[28]	• International, double-blind, placebo-controlled clinical trial exploring the efficacy of intravenous mepolizumab as a corticosteroid-sparing agent for patient with lymphocytic subtype of hypereosinophilic syndrome (L-HES) • Analysis of L-HES was done with T-cell phenotyping63 patients enrolled and 13 met criteria for L-HES ○ 7 received mepolizumab (IV 750 mg) and 6 received placebo	• L-HES participants treated with mepolizumab were more likely to keep a daily prednisone dose ≤10 mg and a lower mean daily dose • Participants treated with mepolizumab were more likely to achieve an eosinophil count below 600/μL for 8 weeks compared to placebo treated participants, but less likely to maintain those levels throughout the trial when compared with patients without L-HES subtype	Mepolizumab can be a useful corticosteroid-sparing method for treating L-HES Some cases maintained eosinophil levels >600 μL despite treatment suggesting overproduction of IL-5 or incomplete antibody neutralization

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