Efficacy of Mepolizumab for the Treatment of Eosinophilic Cystitis: A Report of 2 Cases

Trefond L[1,2], Guy L[3], Darcha C[4], Gallon A[5], Thomas-Monier R[5], Berdugo K[6], Smets P[1], Olagne L[1], Stievenart J[1], Fayard D[1], Cathebras P[7], Aumaitre O[1,2], Boyer L[5], Andre M[1,2], Kahn J-E[6]

[1]*Service de Médecine Interne, CHU Gabriel Montpied, Clermont-Ferrand, France*

[2]*Université Clermont Auvergne, Inserm U1071, M2iSH, USC-INRA 1382, Clermont-Ferrand, France.*

[3]*Service d'Urologie, CHU Gabriel Montpied, Clermont-Ferrand, France*

[4]*Service d'Anatomopathologie, CHU Estaing, Clermont Ferrand, France*

[5]*Service de Radiologie, CHU Gabriel Montpied, Clermont-Ferrand, France*

[6]*National Reference Center for Hypereosinophilic Syndromes, CEREO, Université Paris-Saclay, Assistance Publique - Hôpitaux de Paris, Department of Internal Medicine, Ambroise Paré Hospital, Boulogne-Billancourt, France*

[7]*Service de Médecine Interne, CHU de Saint-Étienne, Saint-Étienne, France*

J Investig Allergol Clin Immunol 2024; Vol. 34(3): 202-204
doi: 10.18176/jiaci.0954

Key words: Hypereosinophilic syndrome. Eosinophilic cystitis. Mepolizumab.

Palabras clave: Síndrome hipereosinofílico. Cistitis eosinofílica. Mepolizumab.

Eosinophilic cystitis (EC) is a rare manifestation in the spectrum of hypereosinophilic syndrome (HES). It is characterized by eosinophilic infiltration of the bladder wall [1]. Incidence is unknown, and only a few cases have been reported. A literature review of 135 patients from the year 2000, including secondary and idiopathic EC, reported urinary frequency, dysuria, pelvic pain, and hematuria as the most frequent symptoms [2]. Peripheral eosinophilia was present in 43% and positive urine culture in 23%. The etiology of EC is mostly iatrogenic, neoplastic, infectious, and postsurgical, although it can be idiopathic. Treatment is not standardized, and cystectomy may be necessary to improve the patient's quality of life.

Mepolizumab is a fully humanized monoclonal antibody that targets human IL-5, thereby blocking the binding of human IL-5 to the IL-5 receptor complex on the surface of the eosinophil. By inhibiting IL-5, mepolizumab reduces the production and survival of eosinophils and suppresses eosinophil-driven inflammation. It is approved in Europe for the treatment of severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, severe chronic rhinosinusitis with nasal polyps, and HES. We report 2 cases in which mepolizumab was effective for treatment of idiopathic EC.

In case 1, a 69-year-old man was referred to the internal medicine department by his urologist after being diagnosed with EC. He had been experiencing episodic hematuria, dysuria, and urinary frequency for the previous 3 years. He also had a history of ulcerative colitis, which had been surgically treated 20 years previously (with no ongoing treatment), and idiopathic chronic inflammatory demyelinating polyneuropathy, which had been treated with IV immunoglobulin 5 years previously.

During the 3 years preceding the diagnosis of EC, the patient underwent 2 transurethral resections of the prostate, several imaging procedures (ultrasound, computed tomography [CT] scan, magnetic resonance imaging), and 2 cystoscopies, with no significant findings in the biopsy sample. He had received multiple courses of antibiotics and approximately 5 courses of corticosteroids per year (each course lasted 2 weeks). Although corticosteroids provided temporary relief, he continued to experience relapses, which significantly impacted his quality of life.

The diagnosis of EC was confirmed based on significant circumferential thickening of the bladder wall with infiltration of adjacent structures (Figure, A) observed on the CT scan, as well as bladder biopsy revealing a substantial eosinophilic infiltrate (Figure, D and E), with up to 200 eosinophils per high-power field (HPF) and no presence of other inflammatory cells. Additionally, there was extension of the inflammatory eosinophil-rich lesions in the prostate tissue samples. Parasitic, neoplastic, and drug-induced causes of EC were ruled out. Laboratory investigations showed eosinophilia (0.66×10^9/L) and an elevated total IgE level (1500 kU/L). Serum levels of vitamin B12, tryptase, and C-reactive protein were within the normal range. Analysis of the lymphocyte phenotype revealed a large $CD8^+CD57^+$ granular lymphocyte population accounting for 6% of total leukocytes, with no evidence of clonal T-cell receptor rearrangement, which was considered unrelated to HES. Urinary cytology revealed 90 eosinophils per 100 cells.

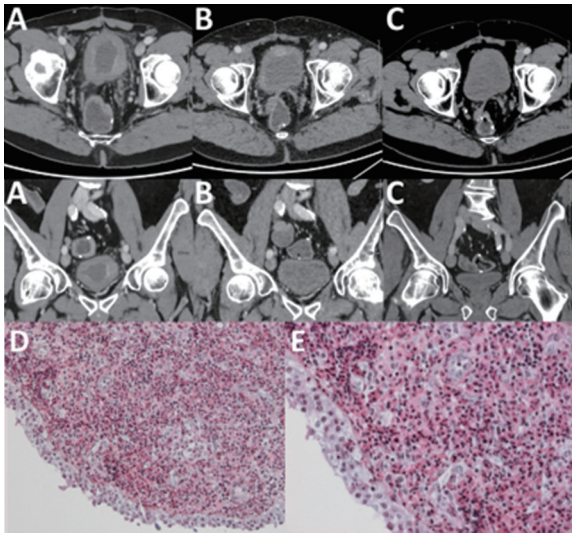

Figure. Computed tomography scan of the first patient prior to initiating mepolizumab (A), at 3 months (B), and at 1 year (C). Urothelial lining with eosinophilic infiltration of the chorion (hematoxylin eosin saffron [HES] × 200 [D], HES ×400 [E]).

To avoid repeated courses of corticosteroids, the patient started subcutaneous mepolizumab 100 mg per month following a 10-day course of corticosteroids. He was informed that this treatment was being used off-label. Three months after starting mepolizumab, the symptoms improved significantly, with no further hematuria or dysuria, and urinary frequency decreased. Urinary cytology revealed 55 eosinophils per 100 cells, and the eosinophil count was 0.09×10^9/L. The CT scan also showed improvement, with only persistence of infiltration in the anterior bladder wall (Figure, B). One year after initiating mepolizumab, the patient remained symptom-free and was no longer taking corticosteroids. A CT scan showed a normal bladder (Figure, C). However, urinary cytology revealed 31 eosinophils per 100 cells. Given the significant improvement in symptoms and CT scan results, no further biopsies were performed.

In case 2, a 14-year-old boy presented with abdominal pain and hypereosinophilia at 7.3×10^9/L. Abdominal ultrasound revealed ileal thickening, leading to a diagnosis of idiopathic eosinophilic enteritis. He was initially treated with a short course of corticosteroids, which resulted in a significant improvement. However, 1 year later, he experienced a relapse with abdominal pain, pollakiuria, and dysuria. Gastric biopsies confirmed the diagnosis of eosinophilic gastroenteritis (EGE) (30 eosinophils per HPF in the small intestine), and a bladder biopsy showed a significant presence of eosinophils (180 eosinophils per HPF) in the chorion along with intravascular eosinophilia. Total IgE levels were elevated (1800 kU/L), while the results of other biological assessments were normal. Corticosteroid treatment was resumed, but the patient relapsed 2 years later, experiencing both digestive and bladder symptoms, with eosinophils reaching 3.0×10^9/L while receiving prednisone 10 mg/d.

The patient was enrolled in a trial involving administration of intravenous mepolizumab at a dosage of 750 mg per month, followed by subcutaneous injections of 300 mg and 100 mg per month. After initiation of mepolizumab, the CT scan at 3 months showed a normal bladder and the patient remained free of relapses for 15 years.

The patients gave permission for their data to be reported here.

The 2 cases we present demonstrate different aspects of EC. The first involved a single organ-restricted eosinophilic inflammation without hypereosinophilia. In the second case, multiple organs were involved (EC and EGE) accompanied by severe hypereosinophilia. However, both cases can be classified as idiopathic HES [1] because there was no underlying cause of hypereosinophilia or evidence of a reactive or neoplastic condition underlying hypereosinophilia and because organ damage can be attributed to hypereosinophilia [1]. This classification is consistent with previous reports in the literature, as EC has not been commonly reported in cases of lymphoid HES [3,5] or clonal HES [5].

To our knowledge, we present the first cases in which mepolizumab was efficacious in treating idiopathic EC.

Given the clinical challenge of finding targeted therapies for EC to avoid the use of corticosteroids and invasive surgical procedures, mepolizumab is a promising option. Previous studies have reported the successful use of mepolizumab in treating other organ-specific HES, such as eosinophilic chronic pneumonia and EGE [6,7].

Three cases of EC successfully treated with another biologic, benralizumab (anti-IL5 receptor), have been reported [8,10]. One was not apparently idiopathic, as the patient had a history of renal cell carcinoma treated with nephrectomy, while the others were idiopathic. None of the patients exhibited blood hypereosinophilia or experienced organ damage resulting from tissue hypereosinophilia. One patient required bilateral nephrostomy, and none of the 3 responded to oral corticosteroids.

These 2 cases suggest that mepolizumab may also be effective in the treatment of EC. This finding encourages further studies on the potential efficacy of mepolizumab in this specific patient population.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

J-E Kahn reports consulting fees for advisory boards from AstraZeneca and GSK, research funding from AstraZeneca and GSK, and participation in clinical trials sponsored by AstraZeneca.

The remaining authors declare that they have no conflicts of interest.

References

1. Valent P, Klion AD, Roufosse F, Simon D, Metzgeroth G, Leiferman KM, et al. Proposed refined diagnostic criteria and classification of eosinophil disorders and related syndromes. Allergy. 2023 Jan;78(1):47-59.
2. van den Ouden D. Diagnosis and management of eosinophilic cystitis: a pooled analysis of 135 cases. Eur Urol. 2000 Apr;37(4):386-94.
3. Carpentier C, Schandené L, Dewispelaere L, Heimann P, Cogan E, Roufosse F. CD3-CD4+ Lymphocytic Variant Hypereosinophilic Syndrome: Diagnostic Tools Revisited. J Allergy Clin Immunol Pract. 2021 Jun;9(6):2426-39.e7.
4. Lefèvre G, Copin MC, Staumont-Sallé D, Avenel-Audran M, Aubert H, Taieb A, et al. The Lymphoid Variant of Hypereosinophilic Syndrome. Medicine (Baltimore). 2014 Oct 2;93(17):255-66.
5. Rohmer J, Couteau-Chardon A, Trichereau J, Panel K, Gesquiere C, Ben Abdelali R, et al. Epidemiology, clinical picture and long-term outcomes of FIP1L1-PDGFRA-positive myeloid neoplasm with eosinophilia: Data from 151 patients. Am J Hematol. 2020 Nov;95(11):1314-23.
6. Wechsler JB, Hirano I. Biological therapies for eosinophilic gastrointestinal diseases. J Allergy Clin Immunol. 2018 Jul 1;142(1):24-31.e2.
7. Delcros Q, Taillé C, Vallée A, Brun AL, Chenivesse C, Couture P, et al. Targeting IL-5/5R for the treatment of idiopathic chronic eosinophilic pneumonia. J Allergy Clin Immunol Pract. 2023;11(4):1317-9.
8. Cooke WD, Cooke AJT. Successful treatment of eosinophilic cystitis with benralizumab. Urol Case Rep. 2020 Aug 11;33:101379.
9. Konstantinou GN, Voukelatou V. Eosinophilic cystitis refractory to steroids successfully treated with benralizumab: A case report. Front Allergy. 2022;3:1055129.
10. Shamriz O, Hershko AY, Talmon A, Ribak Y, Elazary AS, Horev L, et al. The efficacy of off-label IL-5-modulating treatment in rare eosinophil-mediated diseases. Allergol Int. 2021 Apr;70(2):266-8.

Manuscript received July 12, 2023; accepted for publication October 9, 2023.

Ludovic Trefond
Université Clermont Auvergne, Inserm U1071,
M2iSH, USC-INRA 1382
Service de Médecine Interne
CHU Gabriel Montpied Clermont Ferrand
63000 Clermont-Ferrand, France
E-mail: ltrefond@chu-clermontferrand.fr

