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Letter to the Editor

The efficacy of off-label IL-5-modulating treatment in rare eosinophil-mediated diseases

Dear Editor,

Interleukin (IL)-5 is a pivotal factor in eosinophilic inflammation. It promotes eosinophil hematopoiesis, chemotaxis, and activation.¹ The role of IL-5 in the pathogenesis of eosinophilic asthma has been extensively studied and demonstrated in human subjects,² as well in murine models.³ Humanized monoclonal antibodies against IL-5 (mepolizumab and reslizumab) and IL-5 receptor α -subunit (IL-5R α ; benralizumab) have recently been introduced for the treatment of severe eosinophilic asthma. A number of clinical trials have also evaluated the efficacy of IL-5-modulating agents in eosinophilic granulomatosis with polyangiitis (EGPA).⁴ Consequently, subcutaneous administration of mepolizumab is currently approved for use in severe asthma, as well as for EGPA.⁵ Likewise, benralizumab is indicated for severe and refractory eosinophilic asthma in adults, albeit not yet for EGPA.⁶

Eosinophilic disorders, other than asthma, that have also been evaluated for IL-5-modulating therapy include chronic eosinophilic pneumonia and hyper-eosinophilic syndrome.

In spite of the rapidly accumulating data on anti-IL-5/IL-5R α therapy, little is known about its efficacy in numerous other rare disease entities that are deemed eosinophil-mediated.

Therefore, we conducted a retrospective medical record analysis of patients with eosinophilic disorders, who received off-label anti-IL-5 or anti-IL-5R α treatment. Subjects were treated at the Hadassah-Hebrew University Medical Center, Jerusalem, Israel, between January 2017 and December 2019. The medical record of each patient included approval for off-label administration of anti-IL-5 treatment, as issued by the Hadassah Hospital Drug and Therapeutics Committee. This study was approved by the Hadassah Institutional Review Board (IRB number: 0672-18-HMO).

We identified 6 subjects, who received off-label anti-IL-5/IL-5R α monoclonal antibodies for rare eosinophilic disorders (Table 1). This cohort comprised of 4 males and 2 females with ages ranging from 28 to 73 years, at the time of data analysis. The diseases included eosinophilic cystitis, fasciitis, pancreatitis and cholangitis, Kimura's disease, as well as two cases of eosinophilic cellulitis, one of which was congenital. This heterogeneous cohort displayed a wide array of organ system involvement such as the urinary bladder, fascia, skeletal muscle, bone marrow, pancreas, common bile duct, lymph nodes and skin. Likewise, co-morbidities were variable, and consisted metabolic disorders (dyslipidemia and hypertension), steroid-related bone diseases, neoplasm, kidney disease

and hepatitis B virus. The subject with Kimura's disease had asthma, however no allergy or atopy-related co-morbidities were observed in other patients.

All subjects were tested for the presence of auto-antibodies and only 2 had positive results. Rheumatoid factor was detected in the patient with chronic pancreatitis and cholangitis. A borderline ANA result was detected by immunofluorescence in the patient with eosinophilic fasciitis, in accordance with a previous study that reported low positive ANA in up to 25% of patients with this disease.⁷

Tissue biopsies confirming eosinophilic infiltration were found in all 6 patients. The most common biopsies were skin (n = 4) followed by bone marrow (n = 2), urinary bladder (n = 1), pancreas/bile duct (n = 1) and lymph node (n = 1). Of note, diagnosis of eosinophilic fasciitis was also supported by characteristic MRI findings. IL-5-modulating agents were administered to each of the 6 subjects. Mepolizumab was given as an exclusive monoclonal antibody drug to 3 subjects and benralizumab to 2 subjects. In another patient (eosinophilic fasciitis), mepolizumab did not induce complete remission and was subsequently replaced by benralizumab. This, in turn led to clinical resolution and discontinuation of other immunosuppressive drugs.

In all patients, anti-IL-5/IL-5R α treatment required approval as off label use due to the lack of formal indications for this therapeutic modality. Benralizumab was administered at a maintenance dose of 30 mg/8 weeks and mepolizumab at 100 mg/4 weeks. Duration of treatment and follow up periods are detailed in Table 1. In terms of inflammatory markers, reduction was observed in C-reactive protein levels. Four patients disclosed a peak eosinophil count that was considerably elevated ($>3 \times 10^9/L$), and all presented a lower or undetectable count upon the last follow-up visit, under anti-IL-5/IL-5R α treatment. Interestingly, low blood eosinophil counts were already observed under prior GCS treatment and did not change considerably with monoclonal antibodies ($0.26 \times 10^9/L \pm 0.27$ vs. $0.22 \times 10^9/L \pm 0.32$, respectively; $p = 0.8$).

Prior to the administration of IL-5 antagonists all patients had been treated with high doses of prednisone (range: 40–60 mg/day). Other immune-suppressive drugs included cyclosporine A (n = 3), as well as tacrolimus, methotrexate, griseofulvin, dapsone and colchicine (n = 1 each). One subject (congenital eosinophilic cellulitis) disclosed steroid-dependence while the other 5 presented various degrees of resistance to immunosuppressive agents and long-term adverse effects of GCS.

Monoclonal antibody treatments were continued following the reduction in GCS and other immune-suppressive drugs as detailed in Table 1. Concomitantly, all patients presented clinical improvement and none experienced a relapse. Two representative

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Table 1
Subjects with rare eosinophilic diseases: patient characteristics and outcomes of IL-5-modulating treatment.

Patient	1	2	3	4	5	6
Gender/Age (yrs)	M/49	M/59	F/67	M/73	F/28	M/66
Diagnosis	Eosinophilic cystitis	Eosinophilic fasciitis	Chronic eosinophilic pancreatitis and cholangitis	Kimura's disease	Eosinophilic cellulitis, congenital	Eosinophilic cellulitis
Clinical features	Dysuria; pain, pelvic	Leg edema; skin thickening, torso and arms	Abdominal pain	pruritus; fever; lymphadenopathy, inguinal	Diffuse skin lesions	Diffuse skin lesions
Co-morbidities	Hypertension	Dyslipidemia	Whipple surgery, pericarditis, steroid-related vertebral fractures	Minimal change kidney disease, asthma, ca. of prostate, HBV carrier, hypertension	None	Steroid-related avascular necrosis and osteoporosis
Autoantibodies	Negative	ANA (+2/+4) [†]	Rheumatoid factor	Negative	Negative	Negative
Histology (tissue/finding)	Urinary bladder/eosinophilic necrotizing inflammation	Deep skin/eosinophilic myositis; bone marrow/eosinophilia	Pancreas + common bile duct/fibrosis and chronic active eosinophilic inflammation.	Lymph node/preserved architecture with eosinophils; bone marrow/immature eosinophils; skin/eosinophils, fibrosis, asthma	Skin/eosinophilic infiltration of dermis	Skin/eosinophilic infiltration
Monoclonal agent	Benralizumab	Mepolizumab replaced by benralizumab	Benralizumab	Mepolizumab	Mepolizumab	Mepolizumab
Treatment duration (months)	3.1	Mepolizumab, 10.8; benralizumab, 8.6	5.8	0.4	1.6	18.6
Follow-up (months)	7.3	21.4	70.2	35.8	336	139.2
Peripheral eosinophil count x 10 ⁹ /L (peak/last)	0.37/0	4.83/0.01	0.2/0	6.1/0.2	3.1/0.8	4.5/0.36
ESR mm/hr (peak/last)	NA/NA	68/50	22/5	63/16	80/16	52/33
CRP mg/dL (peak/last)	28.4/0.74	6.8/1.83	0.9/0.6	28.46/0.22	10.34/6.16	31.4/7.46
Treatment prior to monoclonals, mg/day	Prednisone, 40	Prednisone, 60; MTX, 20 (week)	Prednisone, 40	Cyclosporine A 100 mg x 2/d; Prednisone, 60	Griseofulvin, Cyclosporin, Dapsone, Colchicine, Prednisone	Prednisone, 60; Cyclosporine A, 300; Tacrolimus, 2
Clinical outcomes and treatment, mg/day, last visit	Clinical and histological remission; GCS discontinued	Clinical improvement; GCS and MTX discontinued	Clinical improvement; GCS discontinued	Clinical improvement, persistent pruritus; GCS discontinued	Resolution of skin manifestations	Immunosuppressive treatment discontinued.

CRP, C-reactive protein; ANA, anti-nuclear antibody; GCS, glucocorticosteroids.

[†] Determined by immunofluorescence and reported as staining intensity on a scale of 1–4.

examples of clinical resolution (eosinophilic cystitis and fasciitis) are depicted in Figure 1. The effect of treatment on the patient with eosinophilic cystitis was manifested by restoration of normal bladder volume, function and histology while in eosinophilic fasciitis resolution of limb edema and discomfort were observed.

The advent of monoclonal antibodies that block IL-5 and eliminate eosinophils has provided a powerful tool for the treatment of eosinophil-mediated inflammatory diseases. When compared to GCS and traditional immune-suppressive drugs, these monoclonal antibodies offer both improved efficacy and excellent safety profiles.⁸ In this study, we present the advantages of IL-5 modulation in rare eosinophilic diseases. These disorders may be disabling and often lack a treatment consensus.⁹ They are generally not considered as an aim for investigation due to the difficulty in recruiting sufficient numbers of subjects. Perhaps the most striking example in this study is the patient with eosinophilic cystitis. This 49-year-old male presented with an inability to retain a sufficient volume of urine leading to continuous leakage. Imaging demonstrated severe thickening of the urinary bladder due to eosinophilic infiltration thus necessitating the insertion of bilateral nephrostomies. Following failure of high-dose prednisone the patient was advised to undergo bladder resection and ileal conduit diversion. However, administration of benralizumab allowed bladder salvage due to prompt clinical and histological resolution. Similarly, IL-5 modulating treatment disclosed an unequivocal improvement in the other five patients and allowed the tapering off of long-term and high-dose GCS treatment.

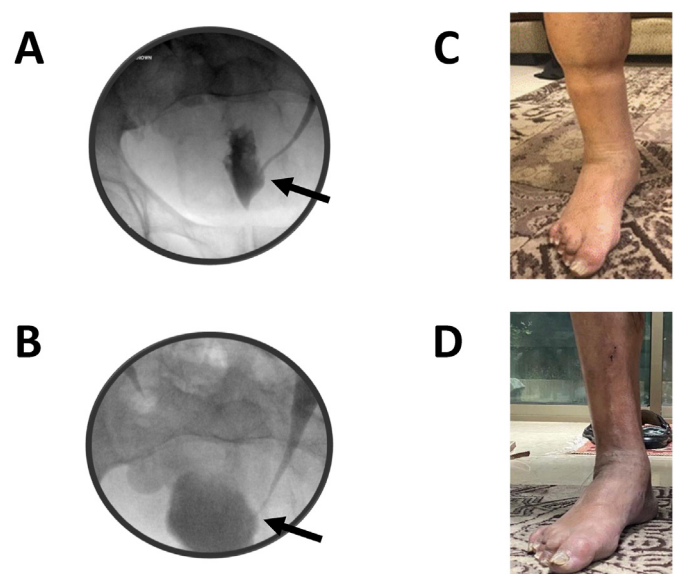


Fig. 1. Representative examples of clinical response to IL-5-modulating treatment in rare eosinophilic disorders. On the left panel are images of cystoscopy of the patient with eosinophilic cystitis. The black arrows indicate the bladder lumen. (A) Imaging prior to administration of benralizumab demonstrating a volume of 40 ml (black arrow) (B) post-treatment showing an increase in volume to 450 ml. On the right panel are pictures of eosinophilic fasciitis taken (C) before and (D) after treatment showing a considerable decrease in limb swelling.

In conclusion, we present a series of patients, who responded well to off-label treatment with mepolizumab and benralizumab. This methodology entails an inherent caveat due to the anecdotal nature of data collection and the lack of statistical power. Nevertheless, it sheds light on various unclear aspects of IL-5 modulation, and may serve as proof-of-concept for potential novel disease targets. Our work shows that anti-IL-5/IL-5R α antibodies may be effective in various rare eosinophil-mediated disorders.

We propose that future studies based on the “basket-trial” methodology,¹⁰ in which a drug is tested on different types of diseases with a common biomarker, may be helpful in eosinophilic disorders. This may be the only practical design for a prospective investigation of IL-5 modulating agents in exceedingly rare diseases.

Conflict of interest

YT is an advisor to GSK and AstraZeneca. The rest of the authors have no conflict of interest.

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References

1. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol* 2013;**132**:1086–96. e5.
2. Brasier AR, Victor S, Boetticher G, Ju H, Lee C, Bleecker ER, et al. Molecular phenotyping of severe asthma using pattern recognition of bronchoalveolar lavage-derived cytokines. *J Allergy Clin Immunol* 2008;**121**:30–7. e6.
3. Shen HH, Ochkur SI, McGarry MP, Crosby JR, Hines EM, Borchers MT, et al. A causative relationship exists between eosinophils and the development of allergic pulmonary pathologies in the mouse. *J Immunol* 2003;**170**:3296–305.
4. Steinfeld J, Bradford ES, Brown J, Mallett S, Yancey SW, Akuthota P, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol* 2019;**143**:2170–7.
5. NUCALA (mepolizumab) for injection. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF. [Accessed 12 April 2020].
6. Fasenra 30 mg solution for injection in pre-filled syringe, benralizumab. <https://www.medicines.org.uk/emc/files/pil.8918.pdf>. [Accessed 14 April 2020].
7. Pinal-Fernandez I, Selva-O' Callaghan A, Grau JM. Diagnosis and classification of eosinophilic fasciitis. *Autoimmun Rev* 2014;**13**:379–82.
8. Kuang FL, Fay MP, Ware J, Wetzler L, Holland-Thomas N, Brown T, et al. Long-term clinical outcomes of high-dose mepolizumab treatment for hypereosinophilic syndrome. *J Allergy Clin Immunol Pract* 2018;**6**:1518–27. e5.
9. Popescu OE, Landas SK, Haas GP. The spectrum of eosinophilic cystitis in males: case series and literature review. *Arch Pathol Lab Med* 2009;**133**:289–94.
10. Park JJH, Hsu G, Siden EG, Thorlund K, Mills EJ. An overview of precision oncology basket and umbrella trials for clinicians. *CA Cancer J Clin* 2020;**70**:125–37.

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