Mepolizumab for refractory eosinophilic fasciitis: a retrospective analysis from two tertiary care centres

Sirs,

Eosinophilic fasciitis (EF) is a rare fibrosing disorder of the fascia characterised by erythema, oedema, and induration of the extremities (1). In the absence of timely and effective treatment, EF can lead to permanent fibrosis and joint contractures and thereby cause significant morbidity (2). Systemic corticosteroids are considered first-line treatment to rapidly mitigate disease activity along with either methotrexate (MTX) or mycophenolate mofetil (MMF) as a corticosteroid-sparing agent (3, 4). However, in the event of treatment-refractory disease, alternative immunosuppressive and/or immunomodulatory therapies are often required, with limited literature available to guide the next steps in treatment.

While the aetiology of EF remains unknown, elevated levels of interleukin (IL)-5 have been implicated in EF pathogenesis (5). IL-5 potentiates the activation and recruitment of eosinophils, which are thought to play a role in both the inflammatory and fibrotic stages of EF (6). Moreover, reported rates of peripheral eosinophilia in EF patients range from 63-93% in the literature, further supporting a potential role for eosinophils in EF pathogenesis (3, 7, 8). As such, we hypothesised that IL-5 antagonism might be a viable therapeutic option for patients with recalcitrant EF.

After obtaining IRB approval, we performed an International Classification of Diseases (ICD-9 and ICD-10) code and natural-language query for medical records from Brigham and Women's Hospital and Massachusetts General Hospital to identify all cases of EF based on biopsy and/or expert opinion from January 2000 through October 2022. Demographics, clinical features, and treatment data were analysed. Three patients treated with mepolizumab, a humanised monoclonal antibody targeting IL-5, were identified: each patient had treatment-refractory EF, having previously trialled MTX, MMF, and/or intravenous immunoglobulin (IVIg) with minimal improvement. Additionally, each patient met criteria for comorbid idiopathic hypereosinophilic syndrome (IHES) due to sustained peripheral eosinophilia and negative work-up for specific myeloproliferative, lymphocytic, or reactive hypereosinophilic syndromes (Table I). Mepolizumab was administered as 300 mg subcutaneous injection every four weeks. In addition to rapid resolution of peripheral eosinophilia, clinical improvement was observed within 2-3 months of treatment initiation in the form of skin softening, improved range of motion (ROM), and pain relief. Additionally, mepolizumab was well tolerated, with headaches being the only reported side effect in one patient.

Herein, we describe the successful treatment of three refractory EF patients with

Table I. Patient characteristics and clinical response to mepolizumab.

Pt	Age (years)/ sex, ethnicity	Areas of involvement	Comorbidities	Peak absolute eosinophil count (cells/ microL)	Disease duration at time of mepolizumab initiation (months)	Prior treatments (mg)	Mepolizumab dose (mg) & frequency	Medications continued at time of mepolizumab initiation (mg)	Time from initiation of mepolizumab to first clinical response (months)	Adverse effects to mepolizumab	Improved function?	Clinical response description	Does the patient remain on mepolizumab?
1	33/M, Black	Bilateral arms, hands, legs, and feet	IHES, seronegative inflammatory arthritis	2,132	15	*Prednisone* 60/d *Methylprednisolone* 1000 infusion/wk x 6 *MMF* 1500 BID *Tofacitinib* 5 BID *Upadacitinib* 30/d	300 subcutaneous injection q4wk	*MMF* 1500 BID *Methylprednisolone* 16/d *Upadacitinib* 30/d	2	Headaches	Yes	Skin softening, increased ROM, improvement in LE pain, able to discontinue SCS and MMF	Yes
2	58/M, White (non-Hispanic)	Bilateral arms and legs, trunk	IHES, asthma	1,642	75	*Prednisone* 60/d *MTX* 25/wk *MMF* 1500 BID *IVIg* 2000/kg x q4wk	300 subcutaneous injection q4wk	*Prednisone* 60/d *MMF* 1500 BID *IVIg* 2000/kg x q4wk	2	None	Yes	Skin softening, increased ROM, improvement in LE pain, able to discontinue SCS and IVIg	Yes
3	54/F, White (non-Hispanic)	Bilateral arms and legs, trunk	IHES, asthma	6,500	12	*Prednisone* 60/d *Methylprednisolone* 1000 infusion/wk x 6 *MMF* 1500 BID *Mycophenolate sodium* 1080 BID *IVIg* 2000/kg x q4wk	300 subcutaneous injection q4wk *sodium*	*Prednisone* 60/d *Mycophenolate* 1080 BID *IVIg* 2000/kg x q4wk	3	None	Yes able to	Skin softening, increased ROM, improvement in LE pain, discontinue SCS	Yes

IHES: idiopathic hypereosinophilic syndrome; d: day; BID: twice daily; wk: week; MMF: mycophenolate mofetil; MTX: methotrexate; IVIg: intravenous immunoglobulin; ROM: range of motion; SCS: systemic corticosteroids; LE: lower extremity.

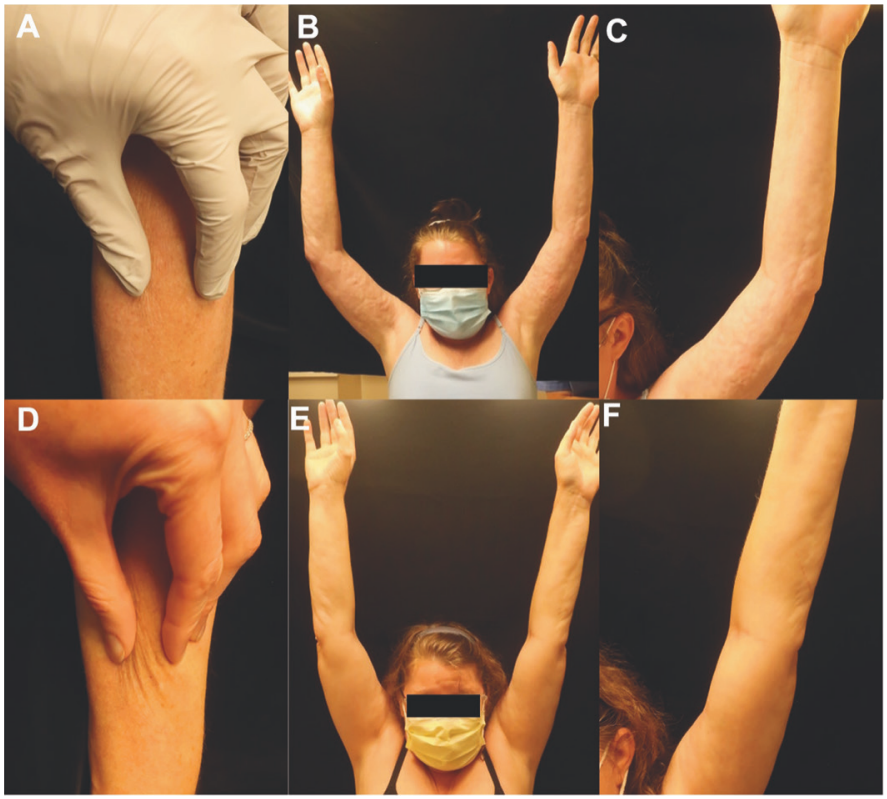

Fig. 1. Representative clinical images before and after 6 months of treatment with mepolizumab.
A 54-year-old woman who presented with rapidly progressive, severe eosinophilic fasciitis experienced minimal improvement despite treatment with pulsed-dose intravenous corticosteroids, mycophenolate mofetil, and intravenous immunoglobulin. Prior to the initiation of mepolizumab, her exam was notable for symmetric, woody induration of her arms (**A**), legs, and trunk with prominent skin dimpling consistent with a "pseudo-cellulite" appearance (**B**), and elbow contractures (**B**-**C**). After six months of treatment with mepolizumab, the patient experienced dramatic improvement in disease activity with increased skin laxity (**D**), resolution of proximal skin dimpling (**E**), and improvement in mobility and joint contractures (**E**-**F**).

mepolizumab. Our cohort complements two prior case reports in the literature describing the utility of IL-5 antagonism in recalcitrant EF (9, 10). Notably, all 5 patients exhibited persistent and marked peripheral eosinophilia prior to initiation of IL-5 antagonism, 4 of the 5 had comorbid asthma, and 3 of the 5 patients met criteria for IHES. Taken together, these features hint at an underlying hypereosinophilic diathesis that may be particularly responsive to IL-5 antagonism. To date, three anti-IL-5 agents have been approved by the U.S. Food and Drug Administration (FDA): reslizumab, benralizumab, and mepolizumab. While the use of reslizumab and benralizumab is typically restricted to those individuals with severe eosinophilic asthma, mepolizumab is approved for use in eosinophilic granulomatosis with polyangiitis, rhinosinusitis with nasal polyps, severe eosinophilic asthma, and hypereosinophilic syndrome. The latter is of particular relevance for the subset of EF patients who exhibit sustained peripheral eosinophilia and meet criteria for comorbid hypereosinophilic syndrome. In this case, mepolizumab can be considered as a therapeutic option, particularly when other systemic treatments have failed to control EF disease activity. While our study is limited by its retrospective nature, small sample size, and lack of a control group, we aim to highlight the disease-modifying potential of IL-5 antagonism in recalcitrant EF and encourage additional clinical and translational studies that further explore these findings.

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