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.

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

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.
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 Ihes. Taken together, these features hint at an underlying hyper eosinophilic 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.

S.N. Sanchez-Meleendez1,2, BS*
K.S. Shaw1, MD*
C.X. Pas1, BA
D.L. Taylor1, MD
N. Shahrir1, MD
D.R. Mazori2, MD**
R.A. Vleugels1, MD, MPH, MBA**

*Co-first authors.
**Co-senior authors.

1Department of Dermatology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA;
2Ponce Health Sciences University, School of Medicine, Ponce, Puerto Rico;
The Ronald O. Perelman Department of Dermatology, NYU Grossman School of Medicine, New York, NY, USA.

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 (F).

References