Letters

RESEARCH LETTER

Mycophenolate Mofetil for Eosinophilic Fasciitis: A Retrospective Analysis From 3 Tertiary Care Centers

Eosinophilic fasciitis (EF) is a fibrosing disorder characterized by edema, erythema, and induration of the extremities. Eosinophilic fasciitis can cause substantial morbidity from joint contractures, and permanent fibrosis may ensue without timely treatment.[1] Corticosteroids are considered first-line therapy; however, long-term treatment with corticosteroid-sparing agents is required to avoid sequelae of chronic steroid use and achieve a durable clinical response.[2] Although methotrexate is often considered the first-line corticosteroid-sparing agent for EF, there is no standardized treatment ladder.[1,3] To our knowledge, 3 cases of EF have reported favorable outcomes with mycophenolate mofetil (MMF) to date.[3,4] Given the paucity of data, we investigated the clinical response of EF to MMF in 3 tertiary care centers.

Methods | After approval by the Partners Healthcare and New York University Grossman School of Medicine institutional review boards, including waiver for informed consent given retrospective deidentified data, we performed a search of the Partners Research Patient Data Registry (January 1979-January 2019; Brigham and Women's and Massachusetts General Hospitals) and 2 medical record databases at New York University Langone Medical Center (January 2005-January 2019) using the terms "eosinophilic fasciitis" and related *International Classification of Diseases, Ninth Revision (ICD-9)* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes, "mycophenolate mofetil," "mycophenolic acid," "myfortic," "cellcept,"and "MMF." Extracted data included demographics, disease presentation, treatments, and clinical response. The 2 senior authors (A.N.F. and R.A.V.) confirmed the diagnosis of EF and assessed clinical response (CR), defined as complete (halted disease progression, resolution of erythema and edema, and improvement of induration), partial (halted disease progression with incomplete improvement of erythema and edema), or no response (continued disease progression). Halting disease progression is the primary goal in treating EF. Although softening of recently involved areas is possible with appropriate treatment, full resolution of induration, particularly in longstanding disease, is rare and not routinely expected. Thus, complete CR was considered halting of disease progression with some improvement of induration, whereas partial CR was defined as improvement in all parameters other than induration. Functional impairment was defined as joint contractures or restricted mobility secondary to EF.

Results | Of 14 patients (8 men and 6 women) with EF treated with MMF, 8 (57%) were treated with MMF given failure or poor tolerance of prior treatment (**Table**). In all but 1 patient (patient 9), MMF served as a steroid-sparing agent and overlapped with systemic corticosteroids, which were subsequently tapered or discontinued. Mean (range) disease duration at treatment initiation was 16.7 (2-60) months. Average daily dose was 2429 mg. Treatment duration ranged from 6 months to 6 years.

By 6 months, 10 patients (71%) had partial and 3 (21%) had complete CR; after 1 year of treatment, 7 (50%) achieved complete CR. Of 12 patients with baseline functional impairment, all experienced improvement after 1 year of treatment with MMF. At the time of most recent follow-up, 5 patients (36%) had partial and 8 patients (57%) had complete CR.

In the 13 patients treated concomitantly with systemic corticosteroids, MMF allowed for corticosteroid discontinuation in 9 (69%) after a median of 13 months of treatment with MMF, with tapering to 10 mg or less of daily prednisone after a median of 3 months. Daily prednisone or equivalent was tapered from a mean of 48 mg to 11.25 mg at most recent follow-up in the remaining 4 patients. In addition, 6 of 9 patients (67%) previously or concurrently receiving other immunomodulators, most commonly methotrexate, were able to discontinue these agents.

Adverse events included gastrointestinal distress in 7 patients, 3 of whom were transitioned to mycophenolic acid with resolution, 3 of whom had mild symptoms that resolved as they continued therapy, and 1 of whom discontinued MMF without trialing mycophenolic acid given a lack of insurance approval. No other adverse events, including infection, were noted.

Discussion | Although often initially responsive to systemic corticosteroids, EF warrants long-term treatment with corticosteroid-sparing agents.[2] In this cohort, all but 1 patient responded favorably to MMF, 5 (36%) achieving partial and 8 (57%) achieving complete CR. The 1 nonresponder was lost to follow-up before receiving 12 months of therapy but was able to lower concomitant systemic corticosteroid and methotrexate doses by 6 months. Importantly, most patients (69%) were able to discontinue concurrent systemic corticosteroids, whereas the remainder were able to taper their doses substantially at the time of most recent follow-up. In addition, MMF was efficacious for both recently diagnosed and longstanding, recalcitrant disease where past therapies failed.

Use of MMF was associated with an immunomodulatory and antifibrotic effect for cutaneous sclerosis in patients with systemic sclerosis in a recent randomized clinical trial, improving modified Rodnan skin index scores.[5] Mycophenolate mofetil is thought to decrease fibroblast activity and collagen synthesis through inhibition of the TGF-β pathway, which plays a prominent role in fibrosis-related diseases.[6] Such evidence supports the use of MMF in other sclerosing skin conditions, including EF. Given increasing data on the efficacy of MMF for cutaneous sclerosis, the authors use MMF not only for pa-

Table. Characteristics and Disease Response to Mycophenolate Mofetil (MMF) in 14 Patients With Eosinophilic Fasciitis

Patient No.[a]	Diagnosis method	Disease duration at initiation MMF, mo	Reason for MMF	Disease distribution	PM	MG	Periph eos	Prior treatment, mg	Medications continued with MMF, mg	Time from MMF start to DC steroids, mo	Time from MMF start to ≤10 mg prednisone	AE to MMF	MMF dose (max daily mg)[b]	MMF treatment duration, mo[c]	Improved funcion	CR at 6 mo	CR at 12 mo
1	Biopsy	12	PTI	UE; LE	Yes	No	No	Prednisone 40/d; MTX 25/wk	None	71	35	GI	3000	72	Yes	Complete	Complete
2	MRI	6	FLSS (EtOH)	LE	No	Yes	No	Prednisone 60/d	None	11	3	GI	2000	36	Yes	Complete	Complete
3	Biopsy, MRI	5	FLSS	UE	No	No	Yes	Prednisone 20/d	None	32	2	No	2500	26	Yes	Partial	Complete
4	Biopsy	36	PTNT	UE; LE	No	No	No	Prednisone 40/d; MTX 25/wk; UV-B	Topical clobetasol	13	5	No	2000	22	Yes	Partial	Complete
5	Clinical	20	PTI	UE; LE	No	Yes	No	Prednisone 60/d; solumedrol; IV MP × 2; MTX 25/wk	None	5	3	No	3000	15	Yes	Partial	Complete
6	MRI	13	PTI	UE; LE	Yes	No	Yes	Prednisone 60/d; MTX 20/wk	None	11	7	GI on MMF; no on MPA	3000	56	Yes	Partial	Complete
7	Biopsy, MRI	12	Family planning	UE; LE	No	No	No	Prednisone 50/d; IV MP × 3; MTX 25/wk	None	15	NA[d]	No	3000	19	Yes	Partial	Complete
8	Biopsy, MRI	30	PTI	UE; LE	Yes	No	Yes	Prednisone 60/d; MTX 25/wk	MTX 17.5; IVIG 1 g/kg ×2 d per mo	54	3	No	2000	61	Yes	Partial	Partial
9	Clinical	60	PTI	UE; LE	No	No	No	MP 12/d; MTX 25/wk SQ	None	NA[d]	NA[d]	GI	2000	14	Not impaired	Partial	Partial
10	Biopsy, MRI	5	FLSS	UE	No	No	No	NA	Prednisone 20/d	NA	NA	GI on MMF; no on MPA	2000	6	Yes	Partial	LTF
11	MRI	17	PTI	UE; LE	No	No	Yes	Prednisone 60/d; MTX 25/wk; MP	MP PO 12/d; MTX 12.5/wk	NA	NA	No	2500	6	Yes	NR	LTF
12	Biopsy, MRI	2	FLSS	UE	No	No	Yes	Prednisone 60/d	Prednisone 10/d	NA	NA	No	2000	6	Not impaired	Complete	NA[e]
13	Biopsy, MRI	6	PTI	LE	No	No	Yes	Prednisone 60/d; HCQ 200 BID; PTX 400 TID	Prednisone 15/d; MTX 10/wk	NA	NA	GI	2000	4	Yes	Partial[f]	Discon-tinued
14	MRI	10	FLSS (EtOH)	UE; LE	No	Yes	Yes	Solumedrol 1 mg/kg ×7; Prednisone 7.5 mg/d; topical clobetasol	None	6	4	GI on MMF; no on MPA	3000	6	Yes	Partial	NA[e]

Abbreviations: AE, adverse effects; BID, twice per day; CR, clinical response; GI, gastrointestinal; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin; LE, lower extremities; LTF, lost to follow-up; MG, monoclonal gammopathy; MP, methylprednisolone; MPA, mycophenolic acid; MRI, magnetic resonance imaging; MTX, methotrexate; NA, not applicable; NR, no response; periph eos, peripheral eosinophilia; PM, plaque morphea; PTX, pentoxifylline; SQ, subcutaneous; UE, upper extremities.

[a] Eight men and 6 women, all white non-Hispanic except 1 African American patient and 1 patient who declined to report.

[b] Dose in MMF equivalents.

[c] Total combined treatment duration with mycophenolate mofetil agent (MMF and/or MPA).

[d] 10 mg or less of prednisone (or equivalent) or discontinued corticosteroids at time of MMF initiation.

[e] Patient not yet treated with therapy for 12 months.

[f] Clinical response at 4 months, after which patient discontinued MMF secondary to gastrointestinal symptoms without trialing MPA.

tients who fail or have a contraindication to methotrexate, but also as first-line corticosteroid-sparing therapy in some patients with moderate-to-severe EF. Although there is no comparative data on the efficacy of methotrexate vs MMF in sclerosing disorders, there is increasing evidence to support the use of MMF given its potential antifibrotic effects in addition to its immunomodulatory properties.[5] Therefore, the authors' standard of care has shifted to using either methotrexate or MMF as first-line corticosteroid-sparing therapy for patients with EF.

Limitations of this study include its retrospective nature, small sample size, and lack of existing outcome measures to assess disease activity in patients with EF. Despite these limitations, this is the largest study of MMF in the treatment of EF, demonstrating the potential efficacy of MMF in this refractory and debilitating orphan disease.

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