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Research Letter

Response to Treatment With Tofacitinib in 11 Patients With Refractory Granulomatosis With Polyangiitis

To the Editor:

Granulomatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic antibody–associated vasculitis that affects mainly small-sized vessels and is characterized by upper and lower respiratory tract, kidney, eye, skin, and neurologic involvement.

The clinical spectrum of GPA includes both granulomatous manifestations, such as lung nodules; orbital masses; ear, nose, and throat involvement; and vasculitic manifestations, such as glomerulonephritis and mononeuritis multiplex.

Although major improvements in the management of GPA have been made previously,[1,2] some patients still experience persistently active disease despite appropriate immunosuppressive therapy and may be classified as having refractory disease.[3] Previous studies have suggested that treatment failure occurs more often in patients with granulomatous disease manifestations than in those with vasculitic manifestations.[4,5]

Tofacitinib (TOF) is a disease-modifying antirheumatic drug that inhibits Janus kinases, thereby suppressing several inflammatory mediators.[6] The successful use of TOF in GPA has recently been reported in a series of 6 patients: 5 with disease relapses and 1 with new-onset disease. None of the patients were described as having refractory disease, only 1 had been treated with rituximab (RTX), and none had received methotrexate (MTX).[7] Moreover, TOF was found superior to MTX in a prospective observational

Table. Characteristics in 11 patients with granulomatosis with polyangiitis treated with TOF for refractory disease.

Patient No.	Sex	Age at Initiation of TOF Therapy, yrs	Disease Duration, yrs	ANCA Status at Diagnosis	Clinical Manifestations	Previous Immunosuppresants	BVAS3 at Initiation of TOF Therapy	BVAS3 at Latest Follow-up[a]	CRP at Initiation of TOF Therapy, mg/L	CRP at Latest Follow-up[a], mg/L	PSL Dose at Initiation of TOF Therapy, mg/d	PSL Dose at Latest Follow-up[a], mg/d	Duration of TOF Therapy, months	TOF Therapy Status at Latest Follow-up
1	F	36	5	PR3	ENT, peripheral nerve, lung nodules with cavitation	RTX, MTX, AZA, MMF, PSL	1	0	24	4	0	0	16	Ongoing
2	F	54	25	MPO	ENT, SGS, EBS, saddle-nose, arthritis	CYC, AZA, MTX, PSL	5	2	18	2	20	0	9	Ongoing
3	M	71	20	PR3	ENT, EBS	CYC, RTX, MMF, TCZ, MTX, PSL	9	2	25	2	12.5	0	23	Ongoing
4	F	69	15	PR3	ENT, SGS, lung nodules	RTX, MMF, MTX, AZA, PSL	9	0	23	2	0	0	19	Ongoing
5	F	53	19	PR3	ENT, saddle-nose, hypophysis	CYC, RTX, MMF, MTX, AZA, IFX	5	0	86	9	0	0	23	Ongoing
6	M	61	19	PR3	ENT, SGS, EBS, lung, skin	CYC, RTX, MMF, PSL	7	7	12	57	37.5	75	22	Discontinued
7	F	33	5	PR3	ENT, SGS, saddle-nose	RTX, MMF, MTX, AZA, PSL	5	0	4	1	12.5	5	16	Ongoing
8	F	55	12	PR3	ENT, lung, nasal septum perforation	CYC, RTX, MMF, MTX, AZA, LEF, PSL	6	0	11	6	37.5	0	23	Ongoing
9	F	22	3	PR3	ENT, nasal septum perforation	CYC, RTX, MMF, MTX, AZA, PSL	6	6	33	13	10	0	23	Discontinued
10	M	50	3	PR3	ENT, lung nodules with cavitation, orbital tumor	CYC, MTX, MMF, RTX, PSL	0	0	22	10	25	20	0	Discontinued
11	M	49	2	PR3	ENT, nasal septum perforation	CYC, RTX, MTX, MMF, PSL	6	6	60	19	12.5	5	7	Discontinued

[a] At latest follow-up or at time of TOF treatment termination, whichever came first. ANCA: antineutrophil cytoplasmic antibody; AZA: azathioprine; BVAS3: Birmingham Vasculitis Activity Score version 3; CRP: C-reactive protein; CYC: cyclophosphamide; EBS: endobronchial stenosis; ENT: ear, nose, and throat; IFX: infliximab; LEF: leflunomide; MMF: mycophenolate; MPO: myeloperoxidase; MTX: methotrexate; PR3: proteinase 3; PSL: prednisolone; RTX: rituximab; SGS: subglottic stenosis; TCZ: tocilizumab; TOF: tofacitinib.

cohort study of 53 patients with Takayasu arteritis (ie, patients suffering from another systemic vasculitic syndrome).[8]

Here, we describe the efficacy and safety of TOF treatment in 11 patients with GPA with predominantly granulomatous disease manifestations. All patients fulfilled the American College of Rheumatology (ACR) 1990 classification criteria for Wegener granulomatosis[9] (now known as GPA) at the time of diagnosis and were followed as part of routine care. Previously, all patients had responded inadequately to immunosuppressive treatment as per the latest ACR guidelines.[3]

All included patients gave oral and written consent to the participation in this work. Off-label use of medicines is allowed in Denmark and does not require approval by an ethics committee.

TOF, at 5 mg doses administered twice daily, was initiated in 7 women and 4 men between May 2020 and January 2022. Patient no. 2, who was treated with MTX for joint involvement, continued this therapy concomitantly with TOF. All other patients discontinued concomitant immunosuppressants except prednisolone (PSL). Each visit included a clinical evaluation using the Birmingham Vasculitis Disease Activity Score version 3 (BVAS3),[10] a measurement of the C-reactive protein (CRP) level, and a review of ongoing treatment with PSL and adverse events.

Patient characteristics are presented in the Table. At baseline, median age was 53 (range 22-71) years, median disease duration was 12 (range 2-25) years, median BVAS3 was 6 (range 0-9), median CRP level was 23 (range 4-86) mg/L, and median PSL dose at TOF initiation was 12.5 (range 0-37.5) mg. The median treatment duration was 19 (range 0-23) months. Patient 10 started TOF because of an orbital mass accompanied by blurred vision, conjunctivitis, and elevated CRP that had not resolved after treatment with RTX. His baseline BVAS3 score was 0 as the symptom duration exceeded 3 months, which is the upper limit for persistently active disease manifestations according to the rules for scoring BVAS3.[10] Four patients discontinued TOF, 3 owing to a lack of clinical efficacy (patients 6, 9, and 11) and 1 because of a pulmonary embolism diagnosed 2 weeks after initiation of TOF therapy (patient 10).

At follow-up, the median BVAS3 had decreased to 0 (range 0-7), the median CRP had decreased to 6 (range 1-57) mg/L, and the median daily PSL dose had decreased to 0 (range 0-75) mg. One adverse event potentially caused by TOF therapy was observed (pulmonary embolism).

In conclusion, the findings presented in this series of 11 patients suggest that TOF may be effective and glucocorticoid-sparing in some patients with refractory GPA and granulomatous disease manifestations. The sample size was too small for any meaningful safety evaluations.

Since our study was performed in a small group of patients with predominantly granulomatous manifestations, it cannot be considered representative for patients with predominantly vasculitic manifestations. Moreover, we did not include patients with new-onset GPA in this case series. However, based on these preliminary observations, these findings warrant confirmation in a larger group of patients with GPA in different phases of the disease.

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The authors declare no conflicts of interest relevant to this article.

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