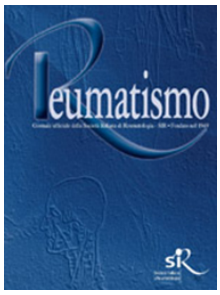

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Baricitinib in polymyalgia rheumatica and giant cell arteritis: report of six cases

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Summary
The objective of this case series is to describe the efficacy and safety of baricitinib (BARI) in a group of patients with polymyalgia rheumatica (PMR) and/or giant cell arteritis (GCA). These patients were treated with BARI due to either a refractory disease course or the unavailability of tocilizumab because of the pandemic.
A total of six patients (five females and one male, median age 64 years, range 50-83) were treated with BARI. Two of them had isolated PMR, two had PMR with associated large vessel (LV)-GCA, one had LV-GCA presenting as fever of unknown origin, and one had cranial-GCA. All patients reported improvement with BARI. At the time of starting BARI, patients were taking a median prednisone dose of 8.75 mg/day (range 0-25), and the four patients with PMR had a median PMR-AS of 23.3 (indicating high disease activity), which decreased to 1.58 after 6 months of treatment with BARI. Two of them could stop glucocorticoids (GC) and continued BARI monotherapy. One patient suffered from pneumonia, and BARI was therefore stopped. No other adverse events attributable to BARI were detected.
Our case series supports previous reports suggesting efficacy of Janus kinase inhibitors as a GC-sparing strategy in PMR and GCA.

Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are two inflammatory, interrelated conditions (1). Glucocorticoids (GC) represent the cornerstone of the treatment but are associated with several adverse effects, and, during the tapering phase of GC, many patients experience relapses of the disease. The current European Alliance of Associations for Rheumatology recommendations suggest adding methotrexate (MTX) in patients with PMR with refractory disease or at high risk for GC-related adverse events (AEs) and adding tocilizumab (TCZ) or MTX in patients with GCA who have experienced or are at high-risk for GC-related AE (2, 3). Despite the efficacy of TCZ, a proportion of patients fail to reach remission, and, in some cases, TCZ has to be discontinued due to AE (4). Janus kinase inhibitors (JAK-i) are a class of immunomodulators that act on the intracellular transduction pathways and are currently used to treat several immune-mediated diseases, including, but not limited to, rheumatoid arthritis, spondyloarthropathies, and inflammatory bowel diseases (5). Compelling pre-clinical and clinical evidence suggests the efficacy of JAK-i in treating large vessel vasculitis (LVV) (6, 7). Herein, we report six patients with PMR and/or GCA successfully treated with baricitinib (BARI).

Patients and Methods

Patients with a clinical diagnosis of PMR and/or GCA treated with BARI were included. All patients retrospectively fulfilled Bird criteria for PMR and/or the 1990 American College of Rheumatology classification criteria for GCA, except for one who presented exclusively with a fever of unknown origin (FUO). Patients received BARI due to either refractory disease to several lines of therapy or the shortage of TCZ, which was entirely deployed to the COVID-19 wards during the first wave of the pandemic. All patients underwent periodic standardized clinical and laboratory examinations. In patients presenting with PMR, the PMR-activity score (AS) was calculated at each visit. Since BARI may have a suppressing effect on inflammatory markers, even though it is less pronounced than that of TCZ, the "clinical" version of PMR-AS (clin-PMR-AS), which does not take into account C-reactive protein (CRP), was also calculated (8). 18F-fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET/CT) was performed in all patients, either at the onset or during the subsequent clinical workup, to detect the presence of LVV or to exclude other diagnoses.

The submission to the Ethics Committee was not required since off-label treatments of single patients are approved on a case-by-case basis by the Health Management Board and the Hospital Pharmacy. Informed consent was obtained after an explanation of the clinical utility and possible side effects of BARI, based particularly on the known safety profile in rheumatoid arthritis.

Case Series

A total of six patients (five females and one male, median age 64 years, range 50-83) were treated with BARI. Two of them had a final diagnosis of isolated PMR (patients #1 and #6), two had PMR with associated LV-GCA (patients #2 and #5), one had LV-GCA (patient #4), and one had cranial-GCA (patient #3). Demographic and clinical characteristics are shown in Table 1. At the time of starting BARI, patients were taking a median prednisone dose of 8.75 mg/day (range 0-25). The four patients suffering from PMR had a median PMR-AS of 23.3 (range 15.16-40.49) and a median clin-PMR-AS of 22.8 (range 15.0-37.0). At the last follow-up visit, the median PMR-AS was 1.1 (range 0.2-30.2), and the median clin-PMR-AS 0.75 (range 0.0-30.0). Out of these four patients, the three still taking BARI had all a PMR-AS<7, indicating remission (Table 1). The detailed clinical history of each patient is reported below.

Case Report 1

Patient #1 has suffered since January 2017 from girdle pain, with prolonged morning stiffness and weight loss, without fever, headache, visual disturbances, or jaw claudication. She was diagnosed with PMR and treated in another center with deflazacort but relapsed several times during GC

tapering. She then received MTX, stopped after 6 weeks due to leukopenia, hydroxychloroquine, without clinical response, and then sulfasalazine. Because of the refractory nature of the disease, she continued to take deflazacort at dosages of 20-30 mg/day until June 2018, when she started BARI at 4 mg/day. She reported a good response and tapered deflazacort to 12 mg/day. After one month, she stopped BARI due to difficulties in obtaining the drug from the pharmacy, given its off-label use. She experienced a new relapse, and deflazacort was increased to 30 mg/day. She came to our attention and underwent FDG-PET/CT, which showed typical (peri)articular uptake consistent with PMR, without signs of LVV. In February 2019, she started BARI again and experienced rapid clinical improvement and was able to withdraw GC after 6 months. After one year of treatment with BARI, it was tapered to 2 mg/day. The patient reported a slight and transient relapse of myalgia after reducing the BARI dose, which resolved spontaneously before the subsequent visit. At the last follow-up visit, she is still in complete remission with BARI 2 mg, without taking GC and with no AEs.

Case Report 2

Patient #2 presented clinically with PMR. FDG-PET/CT showed (peri)articular findings consistent with PMR and pronounced uptake of the femoral and popliteal arteries. The arterial uptake showed a continuous pattern without significant isolated foci; all these features were consistent with vasculitis rather than atherosclerosis. During the treatment with GC, she developed diabetes mellitus. She then received TCZ and MTX without a response. In December 2018, prednisone was stopped for poorly controlled diabetes and the explicit request of the patient. She started BARI as monotherapy in May 2019 and improved as early as one month. After 6 months of treatment, the patient achieved remission, which is still maintained, without the need for GC.

Case Report 3

Patient #3 had a 10-year history of cranial-GCA, which began with temporal headache, jaw claudication, and one episode of amaurosis fugax. She was initially treated with intravenous GC, with rapid improvement. In the ensuing years, she relapsed several times and was treated with MTX, intravenous cyclophosphamide, mycophenolate, and TCZ, all with insufficient response. BARI 4 mg/die was started, and she could gradually taper prednisone from 25 to 10 mg/day in 6 months without reporting fever or headache. After one year of treatment, she felt well while taking prednisone 7.5 mg/day.

Case Report 4

Patient #4 presented with FUO and FDG-PET/CT showed LVV. She was treated with high-dose GC, with good clinical response, but reported several GC-related AEs. She started monthly intravenous TCZ 8 mg/kg, and after the third infusion, she felt well and began to reduce prednisone to 8.75 mg/day. At the end of March 2020, all intravenous and subcutaneous TCZ was deployed to COVID-19 wards. The patient was, therefore, switched to BARI 4 mg/day. She remained clinically stable and tapered prednisone to 5 mg/day, but reported a subtle return of lower limb claudication after about 3 months. This symptom, although very mild, prompted us to ask for a new FDG-PET/CT, which showed LVV, and we decided to stop BARI and restart TCZ. When TCZ was switched to BARI, we did not perform a further FDG-PET/CT because of the absence of clinical manifestations and the massive reduction in the availability of outpatient diagnostic services due to the pandemic. Therefore, it was not possible to determine whether LVV persisted subclinically throughout those months or relapsed after the switch from TCZ to BARI. After restarting intravenous TCZ, she achieved a complete clinical response while continuing prednisone 5 mg/day.

Case Report 5

Patient #5 presented with pain in the girdles and FUO. FDG-PET/CT showed increased uptake at the level of the shoulders and the sternoclavicular joints and increased uptake of the aortic arch, the brachiocephalic trunk, and the subclavian arteries. Prednisone was started with a good clinical

response, but she relapsed several times during GC tapering. MTX was added without efficacy. She was then treated with weekly subcutaneous TCZ, reporting initial improvement. However, after one month, it was no longer available due to the COVID-19 pandemic. She was switched to BARI 4 mg/day and remained clinically stable while further reducing prednisone. However, after 3 months, she complained of fatigue and dyspnoea. She underwent again FDG-PET/CT, which showed pneumonia in the right lung, in addition to a slight reduction in the inflammation of the shoulders and subclavian arteries. BARI was stopped, and after antibiotic treatment, fortnightly TCZ was re-started with good clinical response.

Case Report 6

Patient #6 presented clinically with PMR, confirmed with FDG-PET/CT, without signs of LVV. After starting prednisone, he achieved almost complete resolution of symptoms, which, however, reappeared at every step-down of GC. Subcutaneous MTX was prescribed, but he complained of malaise and diarrhea, and therefore MTX was discontinued. Because of the shortage of TCZ due to the pandemic, treatment with BARI was started with rapid improvement, and the patient was able to taper prednisone to 2.5 mg/day in 4 months. A further taper of GC was tried, but the patient complained of subtle shoulder girdle pain and, therefore, prednisone 2.5 mg/day was continued.

Discussion and conclusions

In our case series, five out of six (83%) patients showed marked improvement with BARI, and four out of six (67%) achieved complete remission. Two patients (50%) were able to discontinue GC, and the other two are receiving low-dose prednisone, 2.5 and 7.5 mg/day, respectively. One of the two patients in GC-free remission was also able to taper BARI to 2 mg/day. Although this cohort is certainly too small to draw definitive conclusions, it includes diverse patients in terms of age and diagnosis, all with refractory diseases.

In a pilot study on patients with relapsing GCA, of whom ten also had PMR, thirteen out of fourteen patients treated with BARI discontinued GC and maintained remission during the 52-week duration of the study (9). In the 12 weeks following BARI discontinuation, however, four out of fourteen (29%) patients relapsed. In a retrospective study, 35 patients with GCA of whom twelve (34%) also presented with PMR, were treated with either BARI, tofacitinib, or upadacitinib, showing remission in more than half; eleven (31%) patients, however, discontinued JAK-i due to primary inefficacy or relapse (7). The preliminary results of a phase III study on upadacitinib in 428 patients with GCA (NCT03725202) showed sustained remission in 46% of those receiving upadacitinib 15 mg *versus* 29% of those receiving placebo (10).

Less data is available on the efficacy of JAK-i in patients with isolated PMR. A comparison of 35 patients with new-onset PMR receiving tofacitinib monotherapy and no GC with 32 patients receiving prednisone demonstrated similar efficacy of the two regimens, with all patients in both groups showing a PMR-AS<10 at 6 months (11). These preliminary data should be confirmed in a larger trial.

There is a compelling rationale for using JAK-i in GCA and PMR: JAK-i, interfere with the effects of several cytokines, including, but not limited to, interleukin (IL)-6, IL-12, IL-23 and interferons (5). This broad action may be particularly useful for the treatment of multifaceted conditions with complex pathophysiology such as GCA and PMR (12, 13). However, the potential efficacy should be balanced against the safety concerns raised by the regulatory agencies on JAK-i (14,15), especially in the age group of patients with PMR/GCA.

In conclusion, our case series supports previous reports suggesting the efficacy of JAK-i as a GC-sparing strategy in PMR and GCA.

References

1. Camellino D, Matteson EL, Buttgereit F, Dejaco C. Monitoring and long-term management of giant cell arteritis and polymyalgia rheumatica. Nat Rev Rheumatol 2020; 16: 481-95.
2. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al. 2015 recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis 2015; 74: 1799-807.
3. Hellmich B, Agueda A, Monti S, Buttgereit F, De Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020; 79: 19-30.
4. Stone JH, Spotswood H, Unizony SH, Aringer M, Blockmans D, Brouwer E, et al. New-onset versus relapsing giant cell arteritis treated with tocilizumab: 3-year results from a randomized controlled trial and extension. Rheumatology 2022; 61: 2915-22.
5. Fragoulis GE, McInnes IB, Siebert S. JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. Rheumatology 2019; 58: i43-54.
6. Rathore U, Thakare DR, Patro P, Agarwal V, Sharma A, Misra DP. A systematic review of clinical and preclinical evidences for Janus kinase inhibitors in large vessel vasculitis. Clin Rheumatol 2022; 41: 33-44.
7. Loricera J, Tofade T, Prieto-Peña D, Romero-Yuste S, de Miguel E, Riveros-Frutos A, et al. Effectiveness of janus kinase inhibitors in relapsing giant cell arteritis in real-world clinical practice and review of the literature. Arthritis Res Ther 2024; 26: 116.
8. Devauchelle-Pensec V, Saraux L, Berthelot JM, De Bandt M, Cornec D, Guellec D, et al. Assessing polymyalgia rheumatica activity when C-reactive protein is unavailable or uninterpretable. Rheumatology 2018; 57: 666-70.
9. Koster MJ, Crowson CS, Giblon RE, Jaquith JM, Duarte-García A, Matteson EL, et al. Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study. Ann Rheum Dis 2022; 81: 861-7.
10. Blockmans D, Penn SK, Setty A, Schmidt W, Rubbert-Roth A, Hauge EM, et al. LBA0001 efficacy and safety of upadacitinib in patients with giant cell arteritis (select-GCA): a double-blind, randomized controlled phase 3 trial. Ann Rheum Dis 2024; 83: 232-3.
11. Ma X, Yang F, Wu J, Xu B, Jiang M, Sun Y, et al. Efficacy and safety of tofacitinib in patients with polymyalgia rheumatica (EAST PMR): an open-label randomized controlled trial. PLoS Med 2023; 20: e1004249.
12. Terrades-Garcia N, Cid MC. Pathogenesis of giant-cell arteritis: how targeted therapies are influencing our understanding of the mechanisms involved. Rheumatology 2018; 57: ii51-62.
13. Camellino D, Giusti A, Girasole G, Bianchi G, Dejaco C. Pathogenesis, Diagnosis and Management of Polymyalgia Rheumatica. Drugs Aging 2019; 36: 1015-26.
14. Paroli M, Becciolini A, Lo Gullo A, Parisi S, Bravi E, Andracco R, et al. Influence of safety warnings on the prescribing attitude of JAK inhibitors for rheumatoid arthritis in Italy. J Clin Med 2024; 13: 3929.
15. Spinelli FR, Conti F, Caporali R, Iannone F, Cacciapaglia F, Steering Committee of the Italian Society of Rheumatology. Janus kinase inhibitors: between prescription authorization and reimbursability. Reumatismo 2023; 75: 1627.

Table 1. Patients' demographic and clinical characteristics at the time of starting baricitinib and at the last follow-up visit. Weeks are counted from the beginning of the treatment with baricitinib.

					Baseline				6 months				Last follow-up							
Patient #	**Sex**	**Age**	**Diagnosis**	**Previous treatment**	**Disease duration (months)**	**GC dose (mg/day)**	**PMR-AS**	**ESR (mm/h) CRP (mg/L)**	**b/ts-DMARD**	**GC dose (mg/day)**	**PMR-AS**	**ESR (mm/h) CRP (mg/L)**	**Week #**	**Clinical status**	**b/ts-DMARD**	**GC dose (mg/day)**	**PMR-AS**	**ESR (mm/h) CRP (mg/L)**	**AEs**	**Notes**
1	F	66	PMR	MTX, HCQ, SSZ	25.5	8.75[a]	40.5	85 34.9	BARI 4 mg	2,5[a]	5	27 1.5	142	Rem	BARI 2 mg	0	0.2	10 0.9	None	
2	F	78	PMR+ LV-GCA	TCZ, MTX	41.8	0	28.8	40 8.2	BARI 4 mg	0	1.33	45 3.3	126	Rem	BARI 4 mg	0	1.05	67 5.5	None	
3	F	61	C-GCA	CYC, MMF, TCZ	119.8	25	N/A	77 43.2	BARI 4 mg	10	N/A	31 2.0	123	Rem	BARI 4 mg	7.5	N/A	46 4.7	None	
4	F	60	LV-GCA	TCZ	16.4	8.75	N/A	6 1.4	TCZ 8 mg/kg monthly	5	N/A	16 10.5	88	Rem	TCZ 8 mg/kg monthly	5	N/A	5 0.5	None	Switched back to TCZ after 3 months
5	F	83	PMR+ LV-GCA	MTX, TCZ	24.4	12.5	15.2	11 1.6	TCZ 162 mg/eow	18.75	5.3	25 3.1	88	HDA	TCZ 162 mg/eow	10	30.2	19 2.0	Pneumonia	Switched back to TCZ after 4 months
6	M	50	PMR	MTX	24.6	5	17.8	18 2.8	BARI 4 mg	1.25	3.0	13 0.4	70	Rem	BARI 4 mg	2.5	1.0	18 1.5	None	

AEs, adverse events; BARI baricitinib; b/ts-DMARD, biological/targeted synthetic disease-modifying anti-rheumatic drug; CYC, cyclophosphamide; C-GCA, cranial giant cell arteritis, eow: every other week; GC, glucocorticoids; HCQ, hydroxychloroquine; HDA, high disease activity; LV-GCA, large-vessel giant cell arteritis; MMF, mycophenolate mofetil; MTX, methotrexate; N/A, not applicable; PMR, polymyalgia rheumatica; PMR-AS, PMR-activity score; Rem, remission; SSZ, sulfasalazine; TCZ, tocilizumab. [a]Patient #1 was taking deflazacort: GC dose is expressed as prednisone equivalent.