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Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study

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Abstract

Background/Purpose: Pre-clinical vascular inflammation models have demonstrated effective suppression of arterial wall lesional T-cells through inhibition of Janus kinase 3 (JAK3) and JAK1. However, JAK inhibition in patients with giant cell arteritis (GCA) has not been prospectively investigated.

Methods: We performed a prospective, open-label, pilot study of baricitinib (4mg/day) with a tiered glucocorticoid entry and accelerated taper in patients with relapsing GCA.

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Conflicts of Interest: Dr. Warrington (principal investigator) and Jane Jaquith (study coordinator) received support from Eli Lilly and Company, paid to the institution, to assist in the completion of this study. No other authors have any financial conflicts of interests associated with this study.

Results: 15 patients were enrolled (11, 73% female) with a mean(SD) age at entry 72.4(7.2) years, median(IQR) duration of GCA of 9 (7, 21) months, and median of 1(1, 2) prior relapse. Four (27%) patients entered the study on prednisone 30 mg/day, 6 (40%) at 20 mg/day, and 5 (33%) at 10mg/day. Fourteen patients completed 52 weeks of baricitinib. At week 52, 14/15 (93%) patients had ≥1 adverse event with the most frequent events including: infection not requiring antibiotics (n=8), infection requiring antibiotics (n=5), nausea (n=6), leg swelling (n=2), fatigue (n=2), diarrhea (n=1). One subject required baricitinib discontinuation due to adverse event. One serious adverse event was recorded. Only 1 of 14 (7%) patients relapsed during the study. The remaining 13 patients achieved steroid discontinuation and remained in disease remission during the 52-week study duration.

Conclusion: In this proof-of-concept study, baricitinib at 4 mg/day was well-tolerated and allowed glucocorticoid discontinuation in most patients with relapsing GCA. Larger randomized clinical trials are needed to determine the utility of JAK inhibition in GCA.

Introduction

Giant cell arteritis (GCA) is the most common primary systemic vasculitides in patients ≥50 years.[1] Glucocorticoids (GCs) have been the primary therapeutic intervention in GCA since their earliest use in the 1950s.[2] Relapse is common occurring in 43–79% of patients with GC tapering or discontinuation.[3–5] Though GCs have shown efficacy, ongoing use is often required with over 40% of patients still on GCs at five years.[4] Unfortunately, long-term use of GCs is associated with significant side effects and between 50–100% of patients have at least one GC-associated adverse event.[3–6] Clinical trials evaluating disease modifying agents and tumor necrosis factor (TNF)-alpha inhibitors have not demonstrated significant benefit.[7–12]

Thus far, only tocilizumab, an interleukin-6 inhibitor, has shown safety and efficacy in relapse reduction and decrease in GC requirements.[13 14] Given tocilizumab is the only currently approved treatment for GCA by the U.S. Food and Drug Administration (FDA) and the European Commission, it has been quickly incorporated in clinical practice and included in recently updated consensus management guidelines.[15 16] While markedly improved compared to GC monotherapy, patients with GCA treated with tocilizumab still have flare rates of 15–26%.[13 14] In addition, clinical trial and observational data have shown that at 12 months of tocilizumab therapy 30%−47% of patients have still not achieved sustained clinical remission.[13 17] Furthermore, the length of treatment required for tocilizumab in GCA remains unknown. In the first clinical trial evaluating intravenous tocilizumab by Villiger and colleagues, 17/20 patients randomized to the treatment arm were in remission at the end of the 52-week study, of which 8 patients (47%) relapsed after a mean of 6.3 months from tocilizumab discontinuation.[14 18] The two-year open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial showed similar findings. Of patients who were in remission following one year of weekly subcutaneous tocilizumab, only 42% remained in tocilizumab-free and glucocorticoid-free remission over the subsequent two years of observation.[19] Even though tocilizumab has dramatically improved the treatment of GCA, additional agents are needed to increase the therapeutic

options, specifically among those for whom tocilizumab is not tolerated or has not allowed achievement of sustained remission.

Janus kinase (JAK) inhibition with tofacitinib (JAK1/JAK3 inhibitor) in patients with refractory Takayasu's arteritis have shown promise in several case reports and small series[20–25]. A pre-clinical vascular inflammation model has demonstrated that JAK inhibition with tofacitinib suppressed innate and adaptive immunity in the arterial wall, particularly through suppression of tissue-resident memory T cells, and additionally further reduced inflammation by inhibition of vasculogenic effector pathways.[26] In addition, interferon-gamma stimulation of the JAK1/JAK2 pathway has been observed to promote macrophage recruitment to *ex vivo* cultured arteries from patients with GCA.[27] Evaluation of JAK inhibition in the clinical management of GCA, on the other hand, is sparse. Among the limited information available, baricitinib (JAK1/JAK2 inhibitor) has been used in two cases of recalcitrant GCA with beneficial outcome.[28 29] The pre-clinical findings and preliminary case report responses demonstrate the biologic plausibility that agents selectively targeting JAK1/JAK2 hold potential promise in GCA. Although a large phase-3 randomized, placebo-controlled trial evaluating upadacitinib (JAK1 selective inhibitor) is ongoing [ClinicalTrials.gov identifier NCT03725202], to date there has been no formal evaluation of safety or efficacy of JAK1/JAK2 inhibition in GCA. The purpose of this study was to evaluate the prospective safety and preliminary efficacy of baricitinib an oral selective JAK1/JAK2 inhibitor in patients with relapsing GCA.

Methods

Study design and patient population

This was a prospective, open-label interventional study of patients with relapsing GCA. Patients were recruited from the division of rheumatology at Mayo Clinic in Rochester, Minnesota, USA. The study was approved by the Mayo Clinic Institutional Review Board (16–008993) and registered in Clinicaltrials.gov (NCT03026504). Study definitions, which were adapted from similar GCA clinical trials, are listed in Table 1.[13 30 31] All patients were required to have a prior confirmed diagnosis of GCA by either temporal artery biopsy and/or confirmatory radiographic evidence of large vessel vasculitis (Table 1). Patients were required to have a physician confirmed relapse of GCA within six weeks of study entry with evidence of active disease. Relapsing patients with severe vascular symptoms, such as active visual ischemia, aortic dissection, critical limb ischemia, myocardial infarction or cerebrovascular event attributable to GCA were excluded. Treatment with the following agents were required to be held prior to baseline study entry: methotrexate (2 weeks), leflunomide (12 weeks), anti-interleukin 6 agent (4 weeks if infusible, 2 weeks if subcutaneous), rituximab (12 months), tumor necrosis factor alpha inhibitor (etanercept 4 weeks, remainder of class 8 weeks), abatacept (8 weeks). Pulse dose methylprednisolone (>100 mg/day) within 8 weeks of baseline was exclusionary as was any prior treatment of tofacitinib or other JAK-STAT inhibitor.

Study medications

During the screening phase (minimum 2 weeks, maximum six weeks) prednisone was increased to achieve symptom control prior to initiation of the study drug and subsequent accelerated GC taper. Three tiers of prednisone dose were allowed for study entry: 10 mg/day, 20 mg/day, or 30 mg/day. The prednisone dose of study entry was commensurate with the prednisone level at which the relapse occurred. For example, patients with a relapse with prednisone doses ≥20 mg but <30 mg/day were allowed to have prednisone increase to at least 30 mg/day, but not to exceed 40 mg/day for symptom control. Similarly, patients with relapse that occurred with prednisone of ≥10 mg/day but <20 mg/day had an increase to at least 20 mg/day but not to exceed 30 mg/day and patients with relapse occurring with prednisone dose of 0 mg to <10 mg/day were allowed a reinstitution or increase in prednisone to at least 10 mg/day but not exceeding 20 mg/day. All patients were required to have a minimum of two weeks of clinical stability at their entry level prednisone dose before study drug initiation and accelerated GC tapering. The accelerated GC taper is outlined in supplementary table S1. GC discontinuation was at week 22, week 19, and week 15 for tiered entry of 30 mg, 20 mg and 10 mg, respectively. Upon study entry, all participants received baricitinib 4mg/day. Baricitinib was dispensed from a central pharmacy. Pill counts were completed at each visit to assess compliance.

Data collection and outcome measures

Laboratory parameters (complete blood count with differential, alanine aminotransferase [ALT], creatinine with eGFR, ESR and CRP), physical examination and disease activity assessment were performed at each visit (weeks 0, 4, 8, 16, 24, 32, 40, 52). Fasting lipid profile was checked at baseline and week 16. The primary outcome was the frequency of adverse events (AE) and serious adverse events (SAE) at week 52. Definition of AE and SAE are listed in supplementary materials table S2. Parameters used for temporary hold and permanent discontinuation of baricitinib are outlined in supplementary materials table S3.

Secondary outcomes included relapse (Table 1) at week 24, relapse at week 52, change in pre-enrollment ESR and CRP compared to week 24 and week 52, comparison of GC dose at enrollment to week 24 and week 52. The Birmingham vasculitis activity score (BVAS) version 3 was assessed at week 0, week 24, and week 52.[32] A patient global assessment was obtained at baseline and each study visit using a visual analog scale of 100 mm length with perceived level of symptoms attributable to GCA from ranging from 0 (none) to 100 (maximum).

Statistical analysis

Descriptive statistics (e.g., means, median, percentages) were used to summarize the data. Paired comparisons of measures at different timepoints were performed using paired t-tests. Measures that were not normally distributed and did not have symmetric differences were compared using sign tests. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Nineteen patients were screened for this study, all of which met the initial inclusion criteria. During the screening phase four patients were excluded: one due to development of active infection requiring antibiotics, one for two consecutive indeterminate tuberculosis tests, and two patients subsequently declined participation due to travel difficulty. No patients were excluded during the screening phase due to lack of clinical stability prior to study entry. Fifteen patients (100% white, 73% female) were enrolled in the study with a mean ± (standard deviation, SD) age at entry of 72.4±7.2 years, a median (interquartile range, IQR) duration of GCA of 9 (7, 21) months, and a median of 1 (1,2) prior relapse before study entry. Mean (±SD) BMI at study entry was 26.3±3.4 kg/m^2. Thirteen (87%) patients had received historical herpes zoster (HZ) live-attenuated viral vaccine prior to screening, one patient received recombinant, adjuvanted HZ vaccine after study entry, and one patient remained unvaccinated. Characteristics at GCA diagnosis and at relapse prior to study entry are listed in Table 2.

All patients had received GC for initial treatment at GCA diagnosis with only one (patient 5) off of prednisone at time of relapse prior to study entry. Other previous agents included methotrexate (2, 13%); cyclophosphamide (1, 7%) and sirukumab (1, 7%). No patient had previously received tocilizumab. Four (27%) patients entered the study on prednisone 30 mg/day, 6 (40%) at 20 mg/day, and 5 (33%) at 10 mg/day (Table 2).

Safety

One patient (patient 1) with baseline chronic kidney disease (entry eGFR 51 mL/min/1.73m^2) had a decline in renal function at week 4 to a level below study threshold for continuation (eGFR 40 mL/min/1.73m^2) and though improvement in renal function occurred with temporary hold (eGFR 48 mL/min/1.73m^2) the patient did not have an increase to a level allowing resumption after 4 weeks of holding and therefore was prematurely withdrawn at week 8. The remaining 14 patients completed all 52 weeks of baricitinib treatment.

At week 52, 14/15 (93%) patients had at least one AE recorded with the most frequent events including: infection not requiring antibiotics (n=8), infection requiring antibiotics (n=5), nausea (n=6), leg swelling (n=2), fatigue (n=2), diarrhea (n=1), abdominal pain (n=1). One patient developed symptomatic HZ which resolved within 2 weeks of holding the study drug and treatment with antiviral, allowing for subsequent re-initiation. Two patients contracted COVID-19 during the study, both with mild symptoms, neither required hospitalization.

Only one patient had a SAE during the study (transient thrombocytopenia <75 $\times 10^9$/L attributed to concomitant use of antiviral). No patients had any of the following during the study: gastrointestinal perforation, major cardiovascular event (MACE) venous thromboembolism (VTE), or severe vascular symptom.

Changes in laboratory parameters at week 24 and week 52 compared to baseline are outlined in Table 3. Compared to week 0, hemoglobin, leukocytes and neutrophils and lymphocytes were lower at week 24 and week 52. At baseline, nine patients were already receiving statin medications for non-GCA indications. Alterations in the cholesterol profile were observed at week 16 with a statistically significant increase in low density lipoprotein (LDL) and decrease in high density lipoprotein (HDL) but triglycerides and total cholesterol were not significantly different (Table 4).

Efficacy

Only 1 of 14 (7%) patients relapsed during the study (same patient at week 24 and week 52). The subject (patient 10) relapsed at week 24 while on 0 mg/day prednisone with recurrent headache, scalp tenderness, PMR and increased inflammatory markers. Baricitinib was continued and prednisone increased to a dose of 20 mg/day which resulted in symptom and laboratory control. Prednisone was then tapered down to 7.5 mg/day by week 52 at which time the second relapse occurred with recurrent headache, fatigue, weight loss and increased inflammatory markers. The remaining 13 patients were able to follow the accelerated GC taper, achieve GC discontinuation, and remained in disease remission during the duration of the 52-week study. No vision loss or severe vascular symptoms were present as a relapse while receiving baricitinib. Additional study outcomes are highlighted in Table 5. ESR and CRP were both significantly lower at week 24 and week 52 compared to pre-enrollment values. Patient global assessment at week 0 (median 20; IQR: 0–50) was also significantly improved at both week 24 (0; 0–10, p=0.022) and week 52 (5; 0–10=0.039). Among patients completing the study, 4/14 (29%) flared during the 12-week follow up period after baricitinib discontinuation.

Discussion

This report constitutes the first prospective trial utilizing an oral JAK1/JAK2 inhibitor in the management of GCA. The results of this open-label pilot study demonstrate baricitinib at a dose of 4 mg/day appeared both safe and potentially effective in the treatment of patients with relapsing GCA.

Baricitinib at a dose of 4 mg/day appeared to have sufficient control over subsequent relapse both during accelerated GC-tapering and also following GC-discontinuation with only one patient (7%) having a flare while receiving study drug. Formal clinical trials in GCA have had varying endpoints and approaches to GC tapering. Among trials with defined, accelerated, GC-tapering regimens completing at or before 28 weeks, the frequency of relapse in the placebo arms has ranged between 68–78%.[8 9 12 13 30] With tiered entry stratification of prednisone dosing, patients starting on 30 mg, 20 mg, and 10 mg discontinued prednisone at weeks 22, 19 and 15, respectively. As such, the current study constitutes the first trial where all patients were tapered off GCs earlier than 24 weeks, resulting in a prolonged time of observation off of concomitant GC therapy. The only other study with discontinuation of planned prednisone dosing at 22–24 weeks was Hoffman *et al.* evaluating adjunct infliximab in patients with newly-diagnosed GCA, which resulted in observed relapse rates of 82% in the study drug arm and 75% in the placebo group.[9]

Compared to patients without a prior relapse, patients with a history of relapse are more likely to have a subsequent relapse.[33] Therefore, the low observed rate of subsequent relapse among patients with known relapsing GCA combined with the accelerated prednisone taper indicate a perceived benefit of baricitinib in control of disease activity and warrant study in a larger clinical setting.

At least one AE was recorded in all but one patient (93%). This frequency is similar to other clinical trials performed in patients with GCA, regardless of treatment or placebo arm.[9 11–13] Specifically, the AE frequency in the tocilizumab GiACTA study was 96–98% in treatment arms and 92–96% in placebo arms, highlighting the high frequency of AEs in patients, in part attributable to GCs.[13] The rates of AEs in this study are similar to those observed in patients receiving baricitinib for rheumatoid arthritis (RA), despite the average age of patients in the current study being 20 years older than patients treated in the RA trials.[34–40] No new forms of treatment emergent AEs were identified among this population.

A reduction in eGFR precluded the study completion in one patient. Alteration in renal function with slight increase in creatinine and reduction in eGFR has been observed at all dosing levels of baricitinib evaluated (i.e. 1 mg, 2 mg, 4mg, and 8 mg daily).[35] Discontinuation due to renal insufficiency has occurred in 5–6% of patients receiving 4 mg/day baricitinib in RA studies; similar to the current report.[38] The overall mean difference in creatinine observed in our study was 0.02 mg/dl at both week 24 and week 52. This mean difference was lower than studies in RA which have shown mean changes of 0.05–0.07 mg/dl at week 24 and 0.086 mg/dl at week 52 in patients receiving 4 mg/day baricitinib.[35–37] Therefore, use of baricitinib in GCA patients with impaired renal function should be monitored closely.

HZ occurred in one patient (7%) during study drug treatment. Rates of HZ in RA studies evaluating baricitinib at doses between 2–8 mg/day range between 1–8%; similar to the frequency observed in our cohort.[36–38 40] HZ in patients with GCA is not unique to treatment with baricitinib. Among clinical trials providing sufficient detail regarding frequency of HZ, 1/20 (5%) patients receiving abatacept, 3/34 (8%) receiving adalimumab, and 2/12 (17%) receiving methotrexate developed infections.[11 30 41] JAK3 inhibition appears to have greater risk of HZ than JAK2 or selective JAK1 inhibition.[42] For RA patients, it is conditionally recommended to vaccinate prior to initiation of tofacitinib (JAK3/JAK1 inhibitor) but guidance on other JAKinibs is limited.[43] The European Alliance of Associations for Rheumatology (EULAR) recommendations considering vaccination against HZ in high-risk patients but does not require vaccination prior to initiation of targeted synthetic disease modifying anti-rheumatic drug.[44] In the current study, the patient developing HZ had received a live-attenuated zoster vaccination after age 60 but had not received a recombinant, adjuvanted zoster vaccine prior to study entry. Larger trials are necessary to assess the relative risk of HZ in the GCA population receiving JAK inhibition and to delineate the appropriate vaccination mitigation strategies among these patients.

In RA cohorts use of baricitinib has been associated with lipid profile alterations including a rise in both HDL and LDL.[35–38 40] In the current study the LDL increased but the HDL decreased from week 0 to week 16; however, there was no significant change in the overall

total cholesterol. It is possible that higher dose glucocorticoids utilized in the current study, in comparison to lower doses used in management of patients with RA, may have resulted in higher baseline lipid concentrations thus attenuating the perceived effect of baricitinib on the cholesterol profile during follow-up. Evaluation in larger cohorts is needed to better understand the impact of baricitinib on cholesterol metabolism in this patient population. Of note, no patient required initiation of lipid-lowering agent during the study based on lipid profile alteration.

Use of JAK inhibition has gained scrutiny among older adults due to concern of possible increased risk of MACE and VTE. Initial trial safety data in RA patients > 50 years of age with at least one cardiovascular risk factor comparing use of tofacitinib to those receiving a tumour necrosis factor inhibitor has led the U.S. FDA to include a boxed warning for tofacitinib indicating a higher risk of MACE and VTE among RA patients.[45] Although, this preliminary data is specific to tofacitinib, the boxed warning has been extended to include upadacitinib and baricitinib. Data pooled from 9 RA studies (3,492 patients with 7,860 patient-years of exposure); however, showed a VTE risk of only 0.5 per 100 patient-years and no increased risk of MACE in RA patients receiving 2-mg or 4-mg daily baricitinib.[46] While no VTE or MACE occurred during treatment with baricitinib in the current study, the sample size is too small extrapolate overall safety in this patient population and thus exploration of JAK1/JAK2 inhibition in this elderly population will require appropriate caution.

SAEs were notably rare in our study, only occurring in one patient with the development of significant thrombocytopenia. This particular SAE was most likely attributable to concomitant antiviral as it occurred temporally after initiation of acyclovir and recovered following cessation. In addition, the patient re-started baricitinib after a 2-week hold and continued for another 32 weeks without further thrombocytopenia developing. Furthermore, thrombocytopenia is uncommon in the use of baricitinib as a dose-dependent increase in platelets has been observed in patients with RA receiving this therapy.[34–37]

This study must be interpreted in the context of its limitations. First, the results require external validation given the single-center nature of this report. Second, this was an uncontrolled, open-label study without blinded clinical assessment and therefore the lack of blinding and a control arm raise the possibility of assessment bias. Objective assessments (laboratory parameters, physical examination findings) and subjective measures (patient and physician global assessments) were utilized to assess response in this study as is in keeping with clinical care and current trial formats. Given improvement was noted among all evaluated domains, the likelihood of results being from assessment bias alone is unlikely. Although BVAS was incorporated as an outcome parameter, the utility of BVAS in measuring disease activity in GCA is admittedly limited.[47] Nevertheless, it is noteworthy that to date there remains no validated disease activity score for GCA, which consequently limits comprehensive objective clinical assessment in this condition. Third, patients evaluated in this study all had relapsing GCA and thus the effect of this treatment on patients with new-onset disease will require formal evaluation. Fourth, patients with severe vascular manifestations present at the time of relapse were excluded and therefore the utility of baricitinib in this sub-group remains yet unknown. Fifth, this study was designed

prior to the approval of baricitinib by the United States Food and Drug Administration which only approved the 2 mg/day dose for RA. The use of the 4 mg/day dose in this study was based on initial pre-approval studies highlighting the 4 mg/day dosing as the optimal dosing for treatment of RA.[35] Therefore, it is not certain whether a 2 mg/day dose provides similar treatment response. Lastly, none of the patients in this study had received or failed tocilizumab prior to study entry. The utility of baricitinib in patients refractory to tocilizumab is unknown and needs to be evaluated.

In conclusion, this single-center, open-label study of 4 mg/day baricitinib in patients with relapsing GCA demonstrated preliminary evidence of both safety and efficacy. Larger double-blind, placebo-controlled studies are warranted to assess the utility of baricitinib in the management of patients with GCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Role of the Study Sponsor:

Eli Lilly and Company provided funding to support the completion of this investigator-initiated study. Eli Lilly and Company had no role in the study design, or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Eli Lilly and Company.

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Key Messages

What is already known about this subject?

*Giant cell arteritis (GCA) is a chronic rheumatic disease with a high frequency of relapse during glucocorticoid tapering.

*Tocilizumab has proven effective in management of GCA, however 15–26% flare while receiving tocilizumab and approximately 50% flare following discontinuation, highlighting an unmet need for additional therapeutics.

What does this study add?

*Baricitinib at a dose of 4 mg was well tolerated and showed preliminary efficacy in patients with relapsing GCA.

How might this impact on clinical practice or future developments?

*Larger clinical trials are needed to assess the utility of JAK-STAT inhibition in the management of GCA.

Table 1:

Study definitions

Terminology	Definition
Confirmed diagnosis of GCA	Fulfillment of all of the following **1** age ≥ 50 years at symptom onset; **2** history of erythrocyte sedimentation rate (ESR) ≥ 50 mm/hr and/or C-reactive protein (CRP) ≥ 10 mg/L; **3** presence of *at least one* of the following symptoms: **i.** unequivocal cranial symptoms of GCA (i.e. new onset localized headache, scalp or temporal artery tenderness, jaw claudication, or other unexplained mouth or jaw pain upon mastication), **ii.** unequivocal symptoms of polymyalgia rheumatica (PMR) defined as shoulder and/or hip girdle pain associated with inflammatory stiffness, **iii.** systemic inflammatory disease in which the presence of the fever (> 38°C for ≥ 7 days), weight loss (> 5 lbs or 10% premorbid weight), and/or night sweats attributable to GCA without other cause identified; and **4** presence of *at least one* of the following: **i.** temporal artery biopsy consistent with GCA, **ii.** evidence of large-vessel vasculitis by advanced arterial imaging, including magnetic resonance angiography (MRA), computed tomography angiography (CTA), positron emission tomography-computed tomography (PET-CT), or evidence of large vessel or temporal artery findings by color Doppler ultrasonography (CDUS).
Relapse/Active disease	Presence of ESR ≥ 30 mm/hr and/or CRP ≥ 10 mg/L and the presence of *at least one* of the following: **a.** unequivocal cranial symptoms of GCA, **b.** unequivocal symptoms of PMR, **c.** other features judged by the clinician to be consistent with GCA or PMR (e.g. fever of unknown origin, unexplained weight loss, fatigue/malaise, etc.) for which no other etiology was identified as causational.
Severe vascular symptom	**1** active visual ischemia (i.e. newly developing transient or permanent vision loss or diplopia), **2** aortic dissection, **3** critical limb ischemia **4** myocardial infarction, or **5** cerebrovascular attack attributable to GCA
Clinical stability	Improvement in, or the absence of, ongoing signs or symptoms attributable to GCA as evidenced by reduction in symptoms and/or improvement in (or normalization of) inflammatory markers.

Table 2:

Characteristics of patients at giant cell arteritis diagnosis and at relapse prior to study entry

Patient	Sex	GCA features at diagnosis	Method GCA diagnosis	Number Relapses	CRP (mg/L) at PSR[a]	ESR (mm/hr) at PSR[a]	GCA features at PSR[a]	SSA at / prior to PSR[a]	Prednisone (mg/day) entry tier
1	M	CSx, HA, PMR, ST	TAB (+) / LVI (−)	3	19.8	7	CSx	---	10
2	M	HA, ST	TAB (+) / LVI (−)	1	21	49	HA, PMR	---	10
3	F	CSx, LVV, PMR	TAB (+) / LVI (+)	2	23.7	71	PMR	CYC, MTX[b]	20
4	F	CSx, LVV, PMR	TAB (−) / LVI (+)	1	34.4	27	CSx, PMR	---	20
5	F	CSx, HA, LVV, PMR, ST	TAB (−) / LVI (+)	2	13.6	62	PMR	SIR[c]	10
6	F	CSx, LVV, PMR	TAB (−) / LVI (+)	1	22.9	22	CSx, progressive LVV[e]	---	20
7	F	CSx, HA, JC, LVV, ST,	TAB (+) / LVI (+)	1	26.1	42	CSx, progressive LVV[e]	---	10
8	M	CSx, LVV, PMR	TAB (ND) / LVI (+)	2	40.6	56	CSx, PMR, progressive LVV[e]	MTX[d]	20
9	F	CSx, HA, JC, LVV, ST	TAB (+) / LVI (+)	2	12.9	33	HA, ST	---	10
10[*]	F	HA, JC, ST, VI	TAB (+) / LVI (−)	1	25.6	46	HA, ST	---	30
11	M	HA, ST, VI	TAB (+) / LVI (−)	2	26	24.4	HA, ST	---	30
12	F	CSx, HA, JC, LC, LVV, PMR, ST, VI	TAB (+) / LVI (+)	2	19.2	17	CSx, PMR, progressive LVV[e]	---	30
13	F	CSx, HA, JC, LVV	TAB (−) / LVI (+)	1	19.3	19	CSx, HA	---	30
14	F	HA, JC, ST, VI	TAB (+) / LVI (−)	1	26.8	14	JC, PMR	---	20
15	F	CSx, HA, JC, LVV, ST	TAB (+) / LVI (+)	1	12.1	51	CSx, HA, PMR	---	20

[a] PSR (pre-study relapse) refers to the relapse immediately prior to study entry

[b] Patient 3: CYC: (oral 2mg/kg/day × 7 months) followed by MTX (oral 15mg/wk × 9 years) stopped 9 months prior to PSR

[c] Patient 5: SIR: (50 mg subcutaneous q4wks × 8 months), stopped 8 months prior to PSR

[d] Patient 8: MTX (oral 20 mg/wk) × 9 months, on treatment at PSR, held 6 wks before entry

[e] Progressive LVV refers to radiographic worsening of existing arterial segment or involvement of new arterial segment by LVV

[*] Patient 10 is the sole patient to relapse during the study (week 24 and week 52)

CSx, constitutional symptoms; CRP, C-reactive protein; CYC, cyclophosphamide; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; HA, headache; JC, jaw claudication; LC, limb claudication; LVI, large vessel imaging [i.e. CTA, MRA, PET, PET-CT]; LVV, large-vessel vasculitis; MTX, methotrexate; ND, not done; PMR, polymyalgia rheumatica; SSA, steroid sparing agent; SIR, sirukumab; ST, scalp tenderness; TAB, temporal artery biopsy; VI, visual ischemia

Table 3:

Laboratory parameter changes comparing week 0, week 24 and week 52 for 14 patients

Laboratory Parameter[a]	Week 0	Week 24	Week 52	Difference Week 24 to Week 0 (95% CI)	p-value	Difference Week 52 to Week 0 (95% CI)	p-value
Hemoglobin (g/dL)	13.4±0.77	12.9±1.14	12.6±1.17	−0.51 (−0.96, −0.06)	0.030	−0.85 (−1.31, −0.39)	0.002
Leukocytes ($x10^9$/L)	9.9±2.7	6.6±1.9	6.0±1.4	−3.34 (−4.74, −1.94)	<0.001	−3.94 (−5.03, −2.85)	<0.001
Lymphocytes ($x10^9$/L)	2.4±0.67	1.7±0.34	1.6±0.41	−0.64 (−1.12, −0.16)	0.012	−0.77 (−1.08, −0.46)	<0.001
Neutrophils ($x10^9$/L)	6.5±2.8	4.0±1.4	3.6±1.1	−2.52 (−4.07, −0.98)	0.004	−2.12 (−4.06, −1.71)	<0.001
Platelets ($x10^9$/L)	290±76	324±129	312±88	34.1 (−20.0, 88.3)	0.20	22.7 (−13.80, 59.23)	0.20
ALT (U/L)	19.8±5.8	20.4±8.1	24.9±12.0	0.57 (−2.60, 3.74)	0.70	5.07 (−1.78, 11.92)	0.13
Creatinine (mg/dL)	0.9±0.13	0.9±0.13	0.9±0.20	0.02 (−0.05, 0.08)	0.59	0.02 (−0.07, 0.12)	0.60
eGFR (ml/ml/1.73m^2)	67.8±11.7	67.1±10.8	67.7±14.8	−1.50 (−7.47, 4.47)	0.60	−0.86 (−8.83, 7.11)	0.82

[a]Mean ±standard deviation

Table 4:

Lipid profile changes comparing baseline (week 0) to week 16 for 14 patients

Laboratory Parameter[a]	Week 0	Week 16	Difference week 16 to week 0 (95% CI)	p-value
Low density lipoprotein (mg/dL)	85.8±21.3	97.6±23.1	11.9 (2.7, 21.0)	0.015
High density lipoprotein (mg/dL)	86.4±21.9	79.9±23.6	−6.5 (−10.6, −2.4)	0.004
Total cholesterol (mg/dL)	193.2±33.8	197.6±29.1	4.4 (−4.0, 12.7)	0.28
Triglycerides (mg/dL)	105.9±46.7	100.2±48.1	−5.6 (−20.2, 8.9)	0.42

[a]Mean ± standard deviation

Table 5:

Study Outcomes

Outcome[a]	**Pre-baricitinib relapse (n=15)**	**Week 0 (n=15)**	**Week 24 (n=14)**	**p-value**[b]	**Week 52 (n=14)**	**p-value**[b]
Prednisone dose, mg/day	---	20 (10,30)	0 (0, 0)	<0.001[e]	0 (0, 0)	0.006[f]
ESR, mm/hr	33 (19, 51)	7 (6, 17)	13 (7, 19)	0.002[c]	10 (5, 17)	0.022[d]
CRP mg/L	22.9 (19.2, 26.1)	3.4 (<3, 6.9)	<3 (<3, <3)	0.002[c]	<3 (<3, 3.1)	<0.001[d]
BVAS	2 (1, 3)	---	0 (0, 0)	0.002[c]	0 (0, 0)	<0.001[d]
Patient global assessment	---	20 (0, 50)	0 (0, 10)	0.022[e]	5 (0, 10)	0.039[f]
Discontinued glucocorticoids	---	---	14/14 (100%)	---	13/14 (93%)	---
Relapse on study drug	---	---	1/14 (7%)	---	1/14 (7%)	---

[a] median (25^{th} percentile, 75^{th} percentile) or n (%)

[b] p-values obtained using sign test

[c] comparison pre-baricitinib relapse value to week 24

[d] comparison pre-baricitinib relapse value to week 52

[e] comparison week 0 value to week 24

[f] comparison week 0 value to week 52