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Treatment failure in giant cell arteritis

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ABSTRACT

Objective Identify predictors of treatment failure in patients with giant cell arteritis (GCA) receiving tocilizumab in combination with glucocorticoids and in patients with GCA receiving only glucocorticoids.

Methods Posthoc analysis of the Giant-Cell Arteritis Actemra trial including 250 patients who received tocilizumab every week plus a 26-week prednisone taper (n=100), tocilizumab every-other-week plus a 26-week prednisone taper (n=49) or placebo plus a 26-week (n=50) or 52-week (n=51) prednisone taper in the intention-to-treat population. Responders for this analysis were patients who maintained remission (no GCA signs/symptoms and no erythrocyte sedimentation rate elevation) through week 52. Treatment failure was defined as inability to achieve remission by week 12 or relapse between weeks 12 and 52. Predictors investigated in univariate and multivariable analyses included patient characteristics, disease-related and treatment-related factors and patient-reported outcomes (PROs).

Results 149 patients received tocilizumab plus prednisone (TCZ/PDN) and 101 received placebo plus prednisone (PBO+PDN). After adjustment for confounders, treatment failure was significantly less likely in the TCZ/PDN group than the PBO/PDN group (OR, 0.2; 95% CI, 0.1 to 0.3; p<0.0001). Risk for treatment failure was significantly higher in women than men in the PBO/PDN group (OR, 5.2; 95% CI, 1.6 to 17.2; p=0.007) but not in the TCZ/PDN group. Predictors of treatment failure in the TCZ/PDN group included lower baseline prednisone doses and worse PROs at baseline.

Conclusion The strongest risk factors for treatment failure in GCA are treatment with prednisone alone and female sex. Lower starting prednisone doses and impaired PROs are associated with failure to respond to tocilizumab.

Trial registration number NCT01791153.

INTRODUCTION

The clinical course of patients with giant cell arteritis (GCA) treated only with glucocorticoids has been complicated by high rates of disease relapse (40%–80% of patients)^{1–4} and frequent glucocorticoid-related toxicity (>85% of cases).^{3,5–7} Interleukin-6 (IL-6) blockade therapy with tocilizumab has improved the outcomes of patients with GCA by decreasing the risk for relapse, reducing the cumulative exposure to glucocorticoids and improving patients' health-related quality of life.^{8–13} Nevertheless, tocilizumab treatment is not successful in all patients, and approximately 25%–30% of them experience relapse while receiving this medication.^{4,11}

Key messages

What is already known about this subject?

- Most patients with giant cell arteritis (GCA) treated with glucocorticoids alone experience disease relapse and develop glucocorticoid-related toxicity, and up to 30% of patients experience relapse while receiving tocilizumab.
- Risk factors for treatment failure have been investigated in patients with GCA treated only with glucocorticoids. However, a consistent profile defining risk for relapse across studies was not observed and findings were discrepant. Virtually nothing is known about the determinants for relapse in patients with GCA treated with tocilizumab.

What does this study add?

- Our analyses demonstrated that patients with GCA receiving tocilizumab in combination with prednisone were six times less likely to experience treatment failure than those receiving prednisone alone.
- Female sex was the strongest risk factor for treatment failure in prednisone only-treated patients, whereas lower prednisone doses and worse patient-reported outcomes at study baseline increased the risk for treatment failure in patients treated with tocilizumab.

How might this impact on clinical practice or future developments?

- Given the absence of biomarkers to assess the risk for disease relapse in GCA, knowledge of epidemiological, clinical and treatment-related variables associated with poor disease outcomes could help clinicians better stratify, treat and monitor patients.
- Women experience treatment failure significantly more often than men when receiving glucocorticoids alone, and tocilizumab might mitigate this risk, whereas the discovery that patient-reported outcomes predicted treatment failure is a hypothesis generating finding that should be further explored in future studies.

Several studies have explored factors associated with disease relapse in patients with GCA treated only with glucocorticoids.^{3,14,15} Identified predictors for treatment failure have included sex,¹⁴ clinical features at disease onset (eg, polymyalgia rheumatica (PMR) symptoms, strong systemic inflammatory response and weight loss),^{3,16,17} certain

comorbidities (eg, diabetes)¹⁴ and increased serum proinflammatory cytokine levels (IL-6 and tumour necrosis factor- α).¹⁸ However, a consistent phenotype associated with treatment failure has not been identified, and results found in some studies have not always been replicated in others.

In contrast, virtually nothing is known about determinants for disease relapse in patients treated with tocilizumab. This problem, coupled with the unreliability of C reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) for disease activity monitoring with IL-6 blockade therapy,^{4,19} makes the longitudinal care of patients with GCA treated with tocilizumab challenging.

Risk stratification of patients with GCA based on clinical predictors may assist clinicians in choosing the most appropriate treatment and monitoring regimens for each case. We aimed to identify predictors of treatment failure in patients with GCA who received prednisone alone or tocilizumab plus prednisone.

METHODS

Study design and participants

We performed a posthoc analysis of data from the randomised, placebo-controlled Giant-Cell Arteritis Actemra (GiACTA) trial (ClinicalTrials.gov, NCT01791153)⁸ to identify predictors of treatment failure because of refractory disease (failure to achieve disease remission over the first 12 weeks) or disease relapse following remission in patients with GCA. Details of the trial design have been published.²⁰ The trial was conducted at 76 centres in 14 countries (see online supplemental appendix 1 for list of investigators). Patients with active disease within 6 weeks of baseline were randomly assigned in a 2:1:1:1 ratio to one of four treatment arms: tocilizumab 162 mg subcutaneously every week plus a 26-week prednisone taper (n=100); tocilizumab 162 mg subcutaneously every other week plus a 26-week prednisone taper (n=50); placebo plus a 26-week prednisone taper (n=50) and placebo plus a 52-week prednisone taper (n=51). The intention-to-treat population consisted of 250 patients because one patient who had been assigned to receive tocilizumab every other week did not receive the trial drug and was excluded from the analysis. For this analysis, the two tocilizumab plus prednisone arms were combined (TCZ/PDN group) and the two placebo plus prednisone arms were combined (PBO/PDN group).

Either glucocorticoid treatment for GCA was initiated or the previously used dose was maintained or modified during screening at the discretion of the investigators. At baseline, patients had to be receiving a daily prednisone dose between 20 mg and 60 mg. From baseline through week 52, the prednisone dose was tapered as determined by the protocol.

Randomisation was performed using an interactive voice response system and was stratified according to whether each patient's baseline prednisone dose was ≤ 30 or > 30 mg/day. Patients were randomly assigned to receive tocilizumab or matching placebo by subcutaneous injection. Prednisone doses between 60 mg and 20 mg were administered open-label, and doses below 20 mg were provided in weekly blister packs for blinded administration with marked daily doses that included prednisone or placebo capsules.

The GiACTA trial was approved by institutional review boards at the institutions involved and was conducted under the guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Outcome definitions and predictors

Treatment response was defined as the achievement and maintenance of clinical remission from week 12 to week 52 with adherence to the protocol prednisone taper. Clinical remission status was determined by the investigators based on the absence of disease activity, defined as GCA signs and symptoms or ESR elevation attributable to GCA that required treatment intensification. The requirement for normalisation of CRP levels to < 1 mg/dL, which was part of the definition of remission for the primary analysis,⁸ was not included in the definition of clinical remission for the current analysis. Treatment failure was defined as failure to achieve clinical remission by week 12 (refractory disease) or relapse of disease activity between week 12 and week 52 after the achievement of clinical remission by week 12.

Potential predictors of treatment failure included demographic and patient characteristics, disease features (eg, new-onset vs relapsing disease, duration of disease, clinical manifestations and levels of inflammatory markers), treatment-related factors (TCZ/PDN vs PBO/PDN treatment group and initial prednisone dose) and patient-reported outcomes (PROs) (online supplemental box 1). The PROs evaluated were Patient Global Assessment of Disease Activity (PtGA) score,²¹ Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale,²² 36-Item Short Form Survey (SF-36)²³ and EuroQol-5D (EQ-5D) score²⁴ (online supplemental table 1). Except for data on clinical manifestations that reflected the time of disease presentation (ie, headache, scalp tenderness, jaw claudication, GCA-related visual loss, PMR symptoms, positive temporal artery biopsy and imaging demonstrating large-vessel vasculitis), all other predictor variables were measured at baseline.

Statistical analysis

All analyses were performed using SAS statistical software. Continuous data were described as means and SD or medians and IQR, and categorical variables were described as absolute frequencies and percentages. The Cochran-Mantel-Haenszel test was used to compare the proportions of patients who experienced treatment failure between the PBO/PDN group and the TCZ/PDN group adjusted for baseline prednisone dose (≤ 30 mg/day or > 30 mg/day). Univariate and multivariable analyses were performed to identify predictors of treatment failure in the entire cohort of patients as well as in the TCZ/PDN and PBO/PDN groups separately. Variables considered for the analyses were initially selected based on current understanding of risk factors for poor treatment outcomes in GCA. Univariate comparisons were made using *t* tests and χ^2 tests for continuous and categorical data, respectively. Logistic regression was used for multivariable analyses and included treatment group and a set of variables chosen based on scientific rationale (new-onset vs relapsing disease, duration of disease, prednisone dose at baseline). Additionally, variables associated with treatment failure in univariate analyses of the entire cohort ($p < 0.05$) were entered in the multivariable models. Multicollinearity was examined using the variance inflation factors. PROs exhibited a high degree of collinearity and therefore were not allowed to enter a logistic regression model simultaneously. Results of the multivariable analyses were reported as estimated ORs for treatment failure, with corresponding 95% CI. All analyses were exploratory, and no adjustment was made for type I error control.

RESULTS

Baseline characteristics of patients in the GiACTA trial cohort²⁵ and the primary analysis⁸ are published. The 250 patients

Table 1 Baseline characteristics of patients with GCA who met criteria for treatment response or failure

	PBO/PDN* (n=94)	TCZ/PDN* (n=130)	All patients* (n=224)
Age, years	68.4 (7.7)	68.9 (8.4)	68.7 (8.1)
Female, n (%)	71.0 (75.5)	98.0 (75.4)	169.0 (75.4)
GCA duration, weeks	43.7 (73.6)	41.9 (78.9)	42.7 (76.6)
Newly diagnosed disease, n (%)	45.0 (47.9)	66.0 (50.8)	111.0 (49.6)
Cranial symptoms only or cranial and PMR symptoms, n (%)	75.0 (79.8)	103.0 (79.2)	178.0 (79.5)
PMR symptoms only, n (%)	19.0 (20.2)	27.0 (20.8)	46.0 (20.5)
Cranial symptoms only, n (%)	33.0 (35.1)	51.0 (39.2)	84.0 (37.5)
Baseline prednisone dose, mg/day, n (%)	35.2 (13.7)	35.7 (13.3)	35.5 (13.4)
Baseline prednisone dose ≤30 mg/day, n (%)	48.0 (51.1)	64.0 (49.2)	112.0 (50.0)
CRP, mg/L	8.0 (16.9)	8.2 (17.0)	8.1 (16.9)
ESR, mm/hour	25.6 (21.4)	23.2 (17.7)	24.2 (19.4)
PtGA, 100 mm VAS	41.4 (28.2)	43.9 (25.6)	42.8 (26.7)
EQ-5D score	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)
FACIT-Fatigue score	33.8 (13.4)	36.5 (11.2)	35.4 (12.2)
SF-36 MCS	41.7 (13.4)	44.7 (12.8)	43.4 (13.1)
SF-36 PCS	42.5 (10.0)	42.8 (8.6)	42.7 (9.2)

Data are shown as mean (SD) unless specified otherwise.

*Does not include the 26 patients (seven TCZ/PDN, 19 PBO/PDN) who were non-responders for reasons other than treatment failure (see supplementary table 2) for reasons for non-response in this group).

CRP, C reactive protein; EQ-5D, EuroQol 5-D; ESR, erythrocyte sedimentation rate; FACIT, Functional Assessment of Chronic Illness Therapy; GCA, giant cell arteritis; MCS, Mental Component Summary; PBO/PDN, placebo+prednisone; PCS, Physical Component Summary; PMR, polymyalgia rheumatica; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short Form Survey; TCZ/PDN, tocilizumab+prednisone; VAS, visual analogue scale.

included in the intention-to-treat analysis (101 in the PBO/PDN group and 149 in the TCZ/PDN group) were 113 treatment responders (45.2%) at week 52, 111 non-responders because of treatment failure (44.4%) (refractory disease or disease relapse) and 26 non-responders because of other reasons (10.4%) (online supplemental table 2). **Table 1** depicts the baseline characteristics of the 224 patients (TCZ/PDN, n=130; PBO/PDN, n=94) defined as treatment responders or treatment failures, excluding the 26 classified as non-responders for reasons other than treatment failure.

Risk for treatment failure

Treatment regimen was the strongest predictor of treatment failure. Treatment response was achieved by 86 patients (66.2%) in the TCZ/PDN group and 27 patients (28.7%) in the PBO/PDN group (**table 2**). Accordingly, rates of treatment failure were significantly lower in the TCZ/PDN group than the PBO/PDN group (33.8% vs 71.3%; $p<0.0001$). In multivariable logistic regression adjusting for disease duration, baseline prednisone dose, previous disease relapse and sex, the OR for treatment

Table 2 Rates of treatment response and treatment failure

	PBO/PDN (n=94)	TCZ/PDN (n=130)	P value*
Treatment response, n (%)	27 (28.7)	86 (66.2)	
Treatment failure, n (%)	67 (71.3)	44 (33.8)	<0.0001
Refractory disease	31 (33.0)	18 (13.8)	
Disease relapse	36 (38.3)	26 (20.0)	

*Cochran-Mantel-Haenszel test comparing the proportions of patients with treatment failure between the PBO/PDN group and the TCZ/PDN group adjusted for baseline prednisone dose (≤30 mg/day or >30 mg/day).

PBO/PDN, placebo+prednisone; TCZ/PDN, tocilizumab+prednisone.

failure in the TCZ/PDN group versus the PBO/PDN group was 0.2 (95% CI, 0.1 to 0.3; $p<0.0001$) (**figure 1A**). In addition, in the TCZ/PDN group, patients receiving ≤30 mg prednisone/day at baseline were at higher risk for treatment failure than those receiving >30 mg/day (OR 2.4; 95% CI, 1.0 to 5.9; $p=0.046$) (**figure 1B**). However, baseline prednisone dose did not predict treatment failure in patients in the PBO/PDN group (**figure 1C**).

In unadjusted analysis of the entire cohort, women accounted for 85.6% of the treatment failures and 65.5% of the treatment responses ($p=0.0005$; **table 3**). When the analysis was limited to each treatment group, results showed that among PBO/PDN-treated patients, women were significantly over-represented in the treatment failure group and under-represented in the treatment response group (86.6% vs 48.1%; $p<0.0001$; **table 4**), but a difference in outcome according to sex was not observed in TCZ/PDN-treated patients. Multivariable analysis confirmed female sex as an independent risk factor for treatment failure among PBO/PDN recipients (OR 5.5; 95% CI 1.6 to 18.7; $p=0.006$) but not among TCZ/PDN recipients (OR 2.3; 95% CI 0.8 to 6.7; $p=0.12$; **Figure 1B,C**). Age, race and body mass index were not associated with treatment outcome (**tables 3 and 4**).

Disease-related features as predictors of treatment failure

Jaw claudication and PMR symptoms at GCA diagnosis were associated with treatment failure in univariate and multivariable analyses of the entire cohort (**table 3**, **figure 1A**). When each treatment group was analysed separately, however, only jaw claudication came close to achieving statistical significance as a clinical feature that independently predicted treatment failure among the TCZ/PDN-treated patients (OR 2.3; 95% CI 1.0 to 5.5; $p=0.06$) (**figure 1B**). In contrast, no clinical manifestations independently predicted treatment failure in the PBO/PDN group (**figure 1C**). Moreover, there were no significant differences in treatment outcome associated with duration of disease, disease type (new-onset vs relapsing disease), baseline level of ESR and CRP or presence of large vessel vasculitis identified by imaging at the time of GCA diagnosis (all $p>0.05$; **tables 3 and 4**; **figure 1**).

Relationship between PROs and treatment failure

Univariate analyses showed that lower baseline health-related quality of life and increased baseline patient perception of disease activity were associated with treatment outcome. In analyses of the entire cohort (**table 3**), PtGA scores were significantly higher (ie, worse) in patients who experienced treatment failure ($p=0.012$). Accordingly, these patients had significantly lower (ie, worse) FACIT-Fatigue ($p<0.0001$), SF-36 Physical Component Summary (PCS) ($p=0.0002$), SF-36 Mental Component Summary (MCS) ($p=0.0023$) and EQ-5D ($p=0.0064$) scores. When treatment groups were analysed separately (**table 4**), a statistically significant association was found between PROs and treatment failure for all PROs ($p<0.05$) except PtGA ($p=0.46$) and EQ-5D ($p=0.14$) in PBO/PDN-treated patients and SF-36 MCS ($p=0.11$) in TCZ/PDN-treated patients.

To explore the independent effect of PROs on treatment outcome while avoiding the problem of collinearity associated with these tools, we constructed logistic regression models that included one PRO at a time. Covariates included in the models were treatment group (TCZ/PDN vs PBO/PDN), baseline prednisone dose, sex, duration of disease, new-onset versus relapsing disease at baseline, PMR and jaw claudication. Baseline PROs independently predicted treatment failure among TCZ/PDN-treated patients but not among PBO/PDN-treated patients

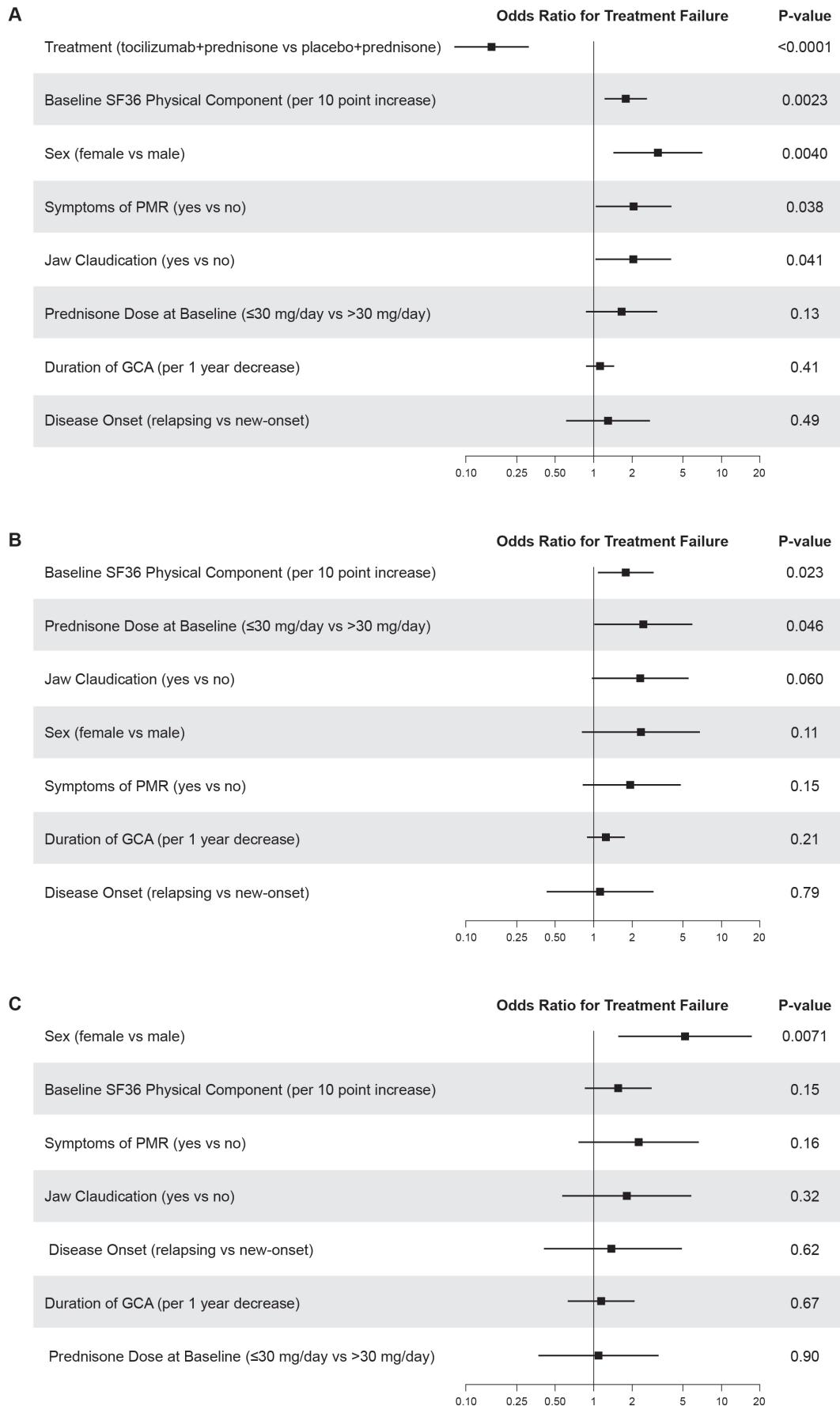


Figure 1 Multivariable analysis of treatment failure (PRO SF-36 Physical Component Summary) for the (A) entire cohort, (B) tocilizumab+prednisone group and (C) placebo+prednisone group. GCA, giant cell arteritis; PMR, polymyalgia rheumatica; PRO, patient-reported outcome; SF-36, 36-Item Short Form Survey.

Table 3 Univariate analysis of treatment failure (intention-to-treat population with treatment outcome defined)

Characteristic	Treatment response (n=113)	Treatment failure (n=111)	P value
Patient-related features			
Age, years, mean (SD)	68.4 (8.3)	68.9 (7.9)	0.64
Female sex, n (%)	74 (65.5)	95 (85.6)	0.00051
White, n (%)	110 (97.3)	109 (98.2)	0.51
BMI, mean (SD)	26.1 (4.3)	25.7 (4.5)	0.52
Disease-related features			
At the time of GCA diagnosis, n (%)			
Headaches	83 (73.5)	70 (63.1)	0.095
Scalp tenderness	40 (35.4)	38 (34.2)	0.85
Jaw claudication	30 (26.5)	44 (39.6)	0.037
GCA-related vision loss	8 (7.1)	10 (9.0)	0.60
PMR symptoms	62 (54.9)	78 (70.3)	0.017
Positive temporal artery biopsy	66/76 (86.8)	71/76 (93.4)	0.17
Imaging demonstrating LVV	56/62 (90.3)	50/61 (82.0)	0.18
At study baseline			
New-onset disease, n (%)	61 (54)	50 (45)	0.18
GCA duration, weeks, mean (SD)	37.9 (75.1)	47.5 (78.1)	0.35
ESR, mm/hour, mean (SD)	22.5 (17.9)	26.0 (20.7)	0.18
CRP, mg/dL, mean (SD)	6.6 (11.2)	9.7 (21.2)	0.17
Treatment-related features			
Baseline prednisone dose, mg/day, mean (SD)	36.0 (13.4)	34.9 (13.5)	0.56
Patient-reported outcomes			
PtGA, mm, mean (SD)	38.4 (26.8)	47.4 (25.9)	0.012
FACIT-Fatigue scale, mean (SD)	39.0 (10.6)	31.7 (12.7)	<0.0001
SF-36 PCS, mean (SD)	44.9 (8.5)	40.4 (9.3)	0.00021
SF-36 MCS, mean (SD)	46.0 (11.8)	40.7 (13.9)	0.0023
EQ-5D score, mean (SD)	0.8 (0.2)	0.7 (0.2)	0.0064

BMI, body mass index; CRP, C reactive protein; EQ-5D, EuroQol-5D; ESR, erythrocyte sedimentation rate; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue scale; GCA, giant cell arteritis; LVV, large vessel vasculitis; MCS, Mental Component Summary; PCS, Physical Component Summary; PMR, polymyalgia rheumatica; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short Form Survey.

(table 5, figure 1). In the TCZ/PDN group, SF-36 PCS and FACIT-Fatigue demonstrated relatively larger effects on treatment outcome with ORs for treatment failure of 1.8 (95% CI 1.1 to 2.9; $p=0.02$) and 1.8 (95% CI 1.2 to 2.6; $p=0.002$), respectively, for every 10-point decrease in a score at baseline (table 5, figure 1B).

DISCUSSION

Treatment failure has major implications for patients with GCA because of disease-associated morbidity and because of the need for additional glucocorticoid therapy, which nearly always leads to treatment-induced toxicity.^{3 5-7 26} The absence of reliable biomarkers to monitor disease activity^{1 4} and to predict treatment failure poses a significant challenge in GCA management. Our analysis identified independent predictors of treatment failure in GCA. These include the use of glucocorticoid monotherapy in general. In addition, a sharp disparity between women

and men was observed among patients treated with prednisone alone: women had a strikingly higher risk for treatment failure, reflected by an OR of 5.2. Among patients randomly assigned to tocilizumab-based regimens, lower initial prednisone doses and worse PROs were significant predictors of treatment failure.

Few studies have explored factors associated with relapse in patients receiving glucocorticoids alone,^{3 14 15} but the identification of a consistent phenotype associated with treatment failure has been elusive. Predictors previously identified include sex,¹⁴ clinical features at disease onset (eg, PMR symptoms and significant weight loss),^{3 16 17} certain comorbidities (eg, diabetes)¹⁴ and increased serum IL-6 levels.¹⁸ Our findings confirm that female sex is a major risk factor for GCA—the disease occurs three times more frequently in women than in men—and a predictor of disease severity.^{14 27 28} We observed that the risk for treatment failure was fivefold higher in women receiving prednisone alone, but the differential response according to sex did not reach statistical significance in women assigned to tocilizumab. Comparison of the risk for treatment failure in women and men assigned to tocilizumab fell short of statistical significance, yet the OR for treatment failure among women was 2.3. These disparities in outcomes defined by sex are noteworthy because, on a per kilogram basis, women received more therapy—glucocorticoids and tocilizumab—than men. Thus, although IL-6 signalling blockade therapy represents a major advance for patients with GCA in general and an important step forward for women with this disease, a crucial unanswered question is why women with GCA are more likely to experience treatment failure with current regimens, particularly glucocorticoids. The finding is not dissimilar to the fact that women are at greater risk for many immune-mediated conditions, such as systemic lupus erythematosus, and that they often have more severe disease courses than men. The basis for these differences in disease expression across the sexes is, in fact, one of the central mysteries of rheumatic disease. In GCA, between-sex genetic differences localised to the X chromosome, the role of sex hormones (although GCA generally occurs in the postmenopausal population) and differences in body composition between women and men are all worthy of further investigation.

Although the introduction of tocilizumab has altered the standard of care for GCA,^{8 9} treatment failure attributed to refractory disease or disease relapse occurs in nearly 30% of patients, which may indicate that inflammatory pathways independent from IL-6 can predominate in some cases. No studies have addressed the risk factors for disease flare among tocilizumab-treated patients. After adjusting for potential confounders, we quantified the therapeutic effect of tocilizumab and observed that its use decreased the risk for treatment failure by approximately fivefold compared with treatment regimens containing prednisone alone. In addition, among patients receiving tocilizumab, baseline prednisone doses lower than 30 mg/day were associated with decreased likelihood of long-term disease control, possibly because in tocilizumab-treated patients starting on higher doses of prednisone, the prednisone tapering schedule dictated that a longer time was needed to reach low prednisone doses, when the risk for flare begins to rise substantially. This longer interval probably permitted more time for the downstream effects of tocilizumab to be fully realised.

In contrast, similar to observations in other studies,^{2 14 16 29} we found no association between treatment outcome and initial glucocorticoid dose in patients treated with prednisone alone. This suggests that the risk for relapse in patients treated with prednisone alone is determined less by the duration of the glucocorticoid taper than by the dose of prednisone a patient is

Table 4 Univariate analysis of treatment failure according to treatment (intention-to-treat population with treatment outcome defined)

	TCZ/PDN response (n=86)	TCZ/PDN failure (n=44)	P value	PBO/PDN response (n=27)	PBO/PDN failure (n=67)	P value
Patient-related features						
Age, years, mean (SD)	68.7 (8.2)	69.2 (8.8)	0.79	67.4 (8.4)	68.8 (7.4)	0.43
Female sex, n (%)	61 (70.9)	37 (84.1)	0.99	13 (48.1)	58 (86.6)	<0.0001
White, n (%)	84 (97.7)	43 (97.7)	0.29	26 (96.3)	66 (98.5)	0.50
BMI, mean (SD)	26.1 (4.4)	25.7 (4.9)	0.66	26.0 (4.1)	25.7 (4.3)	0.72
Disease-related features						
At the time of GCA diagnosis, n (%)						
Headaches	65 (75.6)	28 (63.6)	0.15	18 (66.7)	42 (62.7)	0.72
Scalp tenderness	30 (34.9)	18 (40.9)	0.50	10 (37.0)	20 (29.9)	0.50
Jaw claudication	24 (27.9)	18 (40.9)	0.13	6 (22.2)	26 (38.8)	0.12
GCA-related vision loss	5 (5.8)	4 (9.1)	0.49	3 (11.1)	6 (9.0)	0.75
PMR symptoms	48 (55.8)	31 (70.5)	0.11	14 (51.9)	47 (70.1)	0.093
Positive temporal artery biopsy	50/59 (84.7)	27/27 (100.0)	0.032	16/17 (94.1)	44/49 (89.8)	0.59
Imaging demonstrating LVV	44/49 (89.8)	21/25 (84.0)	0.47	12/13 (92.3)	29/36 (80.6)	0.33
At study baseline						
New-onset disease, n (%)	45 (52.3)	21 (47.7)	0.62	16 (59.3)	29 (43.3)	0.16
GCA duration, weeks, mean (SD)	42.4 (80.8)	40.9 (76.0)	0.92	23.6 (51.2)	51.8 (79.8)	0.093
ESR, mm/hour, mean (SD)	23.6 (18.3)	22.6 (16.7)	0.77	19.1 (16.3)	28.2 (22.7)	0.063
CRP, mg/dL, mean (SD)	6.9 (12.1)	10.9 (23.7)	0.21	5.7 (7.4)	9.0 (19.5)	0.40
Treatment-related features						
Baseline prednisone dose, mg/day, mean (SD)	36.3 (12.9)	34.3 (14.2)	0.42	34.8 (15.2)	35.3 (13.1)	0.88
Patient-reported outcomes						
PtGA: mm, mean (SD)	38.6 (26.4)	54.3 (20.5)	0.0008	38.0 (28.8)	42.8 (28.1)	0.46
FACIT-Fatigue scale, mean (SD)	38.8 (10.8)	32.0 (10.7)	0.0008	39.4 (10.2)	31.6 (13.9)	0.011
SF-36 PCS, mean (SD)	44.2 (8.4)	39.9 (8.3)	0.0076	47.2 (8.7)	40.7 (9.9)	0.0044
SF-36 MCS, mean (SD)	46.0 (11.7)	42.1 (14.6)	0.11	46.4 (12.4)	39.8 (13.4)	0.033
EQ-5D score, mean (SD)	0.8 (0.2)	0.7 (0.2)	0.027	0.8 (0.2)	0.7 (0.2)	0.14

BMI, body mass index; CRP, C reactive protein; EQ-5D, EuroQol-5D; ESR, erythrocyte sedimentation rate; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue scale; LVV, large vessel vasculitis; MCS, Mental Component Summary; PBO/PDN, placebo+prednisone; PCS, Physical Component Summary; PMR, polymyalgia rheumatica; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short Form Survey; TCZ/PDN, tocilizumab+prednisone.

receiving at a particular time. Stated another way, once prednisone is tapered to a certain daily dose (ie, a threshold), the risk for relapse increases, regardless of how long it takes for that dose level to be reached in a patient. Maintaining each patient at a prednisone dose above the flare threshold is likely to reduce the risk for relapse but can cause glucocorticoid toxicity to accumulate if that threshold is sufficiently high. One practical effect of tocilizumab appears to be lowering the prednisone threshold at which GCA flare is likely to occur.

We identified that PROs measuring functional health, well-being and subjective perception of disease activity were independently associated with treatment failure in tocilizumab-treated patients. Why PROs at baseline predicted treatment outcome only in the tocilizumab group is not entirely clear. IL-6 signalling is involved in the pathogenesis of sarcopaenia and frailty,^{30 31} which can contribute to fatigue and other manifestations captured by the PRO instruments used in this study. We hypothesise that impaired health-related quality of life in GCA could reflect higher IL-6 levels that are not fully suppressed by IL-6 signalling blockade once glucocorticoids have been discontinued. Baseline PROs were measured for most patients when they were receiving high doses of prednisone to control their disease activity before they enrolled in GACTA. It seems

logical, therefore, that patients whose PRO scores were impaired despite high-dose prednisone treatment would be at greater risk for treatment failure during the trial. In contrast, because most patients receiving only glucocorticoids during the trial experienced treatment failure, PROs could not discriminate between two putative IL-6 states. Additionally, low statistical power attributed to the small sample size of the PBO/PDN group may, in part, explain the lack of association between PRO measures and treatment failure in patients receiving prednisone alone. The association between PRO scores and increased risk for treatment failure in tocilizumab-treated patients might also be driven by other disease mechanism pathways independently of IL-6.

Our study has certain limitations. First, it was a posthoc analysis of data from a clinical trial that was not specifically powered for the comparisons of interest. Second, because the two groups assessed in this exploratory analysis were different from those originally randomly assigned, bias from unevenly distributed unknown covariates could have been introduced. Nevertheless, our multivariable analyses accounted for the most important known confounders. Finally, the urgency with which GCA must be treated to prevent blindness precluded the collection of samples from patients with untreated active disease to measure inflammatory markers, including IL-6 levels. In fact,

Table 5 Multivariable analysis of PRO measures as predictors of treatment failure

	OR	95% CI	P value
SF-36 PCS (per 10-point decrease)			
All patients	1.8	1.2 to 2.6	0.0023
TCZ/PDN group	1.8	1.1 to 2.9	0.023
PBO/PDN group	1.6	0.9 to 2.8	0.15
FACIT-Fatigue scale (per 10-point decrease)			
All patients	1.6	1.2 to 2.2	0.00081
TCZ/PDN group	1.8	1.2 to 2.6	0.0028
PBO/PDN group	1.3	0.8 to 2.1	0.27
PtGA (per 10-point increase)			
All patients	1.2	1.0 to 1.3	0.028
TCZ/PDN group	1.3	1.1 to 1.5	0.0078
PBO/PDN group	1.0	0.8 to 1.2	0.99
SF-36 MCS (per 10-point decrease)			
All patients	1.3	1.0 to 1.7	0.040
TCZ/PDN group	1.3	1.0 to 1.8	0.090
PBO/PDN group	1.2	0.8 to 1.9	0.42
EQ-5D score (per 0.1-point decrease)			
All patients	1.2	1.0 to 1.4	0.063
TCZ/PDN group	1.2	1.0 to 1.5	0.038
PBO/PDN group	1.0	0.8 to 1.3	0.85

Each model included a single PRO and the following predictor variables: duration of disease at baseline, prednisone dose at baseline, new-onset vs relapsing disease at baseline, sex, PMR symptoms at GCA diagnosis, jaw claudication at GCA diagnosis and (for analysis of all patients) PBO/PDN vs TCZ/PDN treatment.

EQ-5D, EuroQol-5D; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue scale; GCA, giant cell arteritis; MCS, Mental Component Summary; PBO/PDN, placebo+prednisone; PCS, physical component summary; PMR, polymyalgia rheumatica; PRO, patient-reported outcome; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short Form Survey; TCZ/PDN, tocilizumab+prednisone.

most patients were already in glucocorticoid-induced remission before the baseline visit.⁴ Therefore, the key question of whether impaired PROs at baseline were directly related to stronger inflammatory responses or higher IL-6 levels could not be tested. Along those lines, the fact that nearly all patients in the trial were started on prednisone during the screening period or even before the screening period—a measure that was appropriate and necessary—means that our ability to analyse the relationship between the level of the inflammatory state as reflected in baseline acute-phase reactants was limited. Future studies might aim to target this question more specifically, though obtaining samples from large numbers of patients before glucocorticoid therapy begins is challenging because of the urgency with which treatment must be initiated in GCA.

Our study has several strengths. First, our results were derived from prospectively collected data from the largest randomised, double-blind, placebo-controlled clinical trial in GCA.⁸ During the trial, the prednisone taper was standardised and prednisone doses lower than 20 mg/day were administered in a blinded manner to prevent bias.³² Second, our definition of relapse aligns with that commonly used in clinical practice, which includes the presence of clinical signs or symptoms of GCA with or without increased ESR levels necessitating treatment.^{3 14 17} Of note, most relapses in this study were diagnosed after the manifestation of clinical signs or symptoms, with or without concomitant ESR elevation, and only nine relapses were determined based on the presence of an isolated elevation in ESR. Third, this is the first study to analyse predictors of treatment failure in patients with

GCA receiving tocilizumab-based regimens, which are becoming the standard of care in this disease and for which more research is needed.

In summary, we identified important risk factors for treatment failure in GCA, the two strongest of which are prednisone monotherapy and female sex. Future studies might focus on elucidating the reasons for the striking disparity between men and women in risk for treatment failure, and future clinical trials must analyse in detail the impact of sex on treatment outcome.

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Correction notice This article has been corrected since it published Online First. Figure 1 has been replaced.

Contributors Conceptualised and designed study: SHU, YL, JHS. Acquired data: SHU, MB, JHS. Analysed and interpreted data: SHU, MB, JH, YL, AP, JHS. Drafted manuscript: SHU, MB. Critically revised manuscript for important intellectual content: All authors. Approved submission of the manuscript for publication: All authors

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Qualified researchers may request access to individual patient level data through the clinical study data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are available here (<https://vivli.org/members/ourmembers/>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Box 1 Parameters tested as predictors of treatment failure**1. Patient-related features**

Age

Sex

Race

Body mass index

2. Disease-related features*At the time of GCA diagnosis*

Headaches

Scalp tenderness

Jaw claudication

GCA-related vision loss

Polymyalgia rheumatica symptoms

Temporal artery biopsy positive

Imaging demonstrating lesions compatible with large vessel vasculitis^a*At study baseline*

New-onset disease

Disease duration

Erythrocyte sedimentation rate

C-reactive protein level

3. Treatment-related features

Baseline prednisone dose

4. Patient-reported outcomes

Patient Global Assessment of Disease Activity

Functional Assessment of Chronic Illness Therapy–Fatigue score

36-Item Short Form Survey physical component summary

36-Item Short Form Survey mental component summary

EuroQol-5D score

^aImaging included computed tomography angiography, magnetic resonance angiography, and positron emission tomography

Table 1 GiACTA study definitions of patient-reported outcomes

Instrument	Description
Patient Global Assessment of Disease Activity (PtGA)	The PtGA score reflects patients' perceptions of their disease activity, ¹ which is marked on a numerical scale (0-100 mm). Higher numbers indicate perception that disease activity is worse.
Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale	The FACIT-Fatigue scale is a 13-item tool that measures a patient's level of fatigue during their usual daily activities in the past week. ² Fatigue and its impact on physical activity, functionality and social interactions are measured on a four-point Likert scale. The FACIT-Fatigue scale ranges from 0 to 52. Lower numbers indicate worse fatigue and greater impact of fatigue on physical, functional and social outcomes.
36-Item Short Form Survey (SF-36)	The SF-36 is a 36-item, patient-reported survey of functional health and well-being that captures data related to eight health domains (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to emotional problems, emotional well-being, social functioning, energy/fatigue and perception of general health). ³ The SF-36 scores range from 0 to 100. Lower scores indicate less favourable health states.

EuroQol-5D (EQ-5D) score	The EQ-5D is a standardised instrument for measuring generic health status that gathers data regarding patient mobility, self-care, pain, depression/anxiety and usual activities (e.g. work, study, housework and family or leisure activities). ⁴ The EQ-5D score ranges from 0 to 1. Lower numbers indicate worse health status.
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Table 2 Causes of nonresponse to treatment

Cause, n (%)	PBO/PDN	TCZ/PDN
	N=101	N=149
Treatment failure	67 (66.3)	44 (29.5)
Refractory disease	31 (30.7)	18 (12.1)
Disease relapse	36 (35.6) [†]	26 (17.4) [‡]
Other	7 (6.9)	19 (12.8)
Treatment discontinuation because of an adverse event	3 (3.0)	8 (5.4)
Nonadherence to the protocol prednisone taper	1 (1)	4 (2.7)
Study withdrawal before week 52	2 (5.2)	4 (2.7)
Miscellaneous*	1 (1)	3 (2.0)

*Miscellaneous reasons included protocol violation and protocol noncompliance.

[†]Relapse in eight patients was based on isolated elevation of erythrocyte sedimentation rate.

[‡]Relapse in one patient was based on isolated elevation of erythrocyte sedimentation rate.

PBO/PDN, placebo + prednisone; TCZ/PDN, tocilizumab + prednisone.

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Instrument	Description
Patient Global Assessment of Disease Activity (PtGA)	The PtGA score reflects patients' perceptions of their disease activity, ¹ which is marked on a numerical scale (0-100 mm). Higher numbers indicate perception that disease activity is worse.
Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale	The FACIT-Fatigue scale is a 13-item tool that measures a patient's level of fatigue during their usual daily activities in the past week. ² Fatigue and its impact on physical activity, functionality and social interactions are measured on a four-point Likert scale. The FACIT-Fatigue scale ranges from 0 to 52. Lower numbers indicate worse fatigue and greater impact of fatigue on physical, functional and social outcomes.
36-Item Short Form Survey (SF-36)	The SF-36 is a 36-item, patient-reported survey of functional health and well-being that captures data related to eight health domains (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to emotional problems, emotional well-being, social functioning, energy/fatigue and perception of general health). ³ The SF-36 scores range from 0 to 100. Lower scores indicate less favourable health states.

EuroQol-5D (EQ-5D) score	The EQ-5D is a standardised instrument for measuring generic health status that gathers data regarding patient mobility, self-care, pain, depression/anxiety and usual activities (e.g. work, study, housework and family or leisure activities). ⁴ The EQ-5D score ranges from 0 to 1. Lower numbers indicate worse health status.
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Table 2 Causes of nonresponse to treatment

Cause, n (%)	PBO/PDN	TCZ/PDN
	N=101	N=149
Treatment failure	67 (66.3)	44 (29.5)
Refractory disease	31 (30.7)	18 (12.1)
Disease relapse	36 (35.6) [†]	26 (17.4) [‡]
Other	7 (6.9)	19 (12.8)
Treatment discontinuation because of an adverse event	3 (3.0)	8 (5.4)
Nonadherence to the protocol prednisone taper	1 (1)	4 (2.7)
Study withdrawal before week 52	2 (5.2)	4 (2.7)
Miscellaneous*	1 (1)	3 (2.0)

*Miscellaneous reasons included protocol violation and protocol noncompliance.

[†]Relapse in eight patients was based on isolated elevation of erythrocyte sedimentation rate.

[‡]Relapse in one patient was based on isolated elevation of erythrocyte sedimentation rate.

PBO/PDN, placebo + prednisone; TCZ/PDN, tocilizumab + prednisone.

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