CLINICAL SCIENCE

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 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.3,6–11 Nevertheless, tocilizumab treatment is not successful in all patients, and approximately 25%–30% of them experience relapse while receiving this medication.6–11 Several studies have explored factors associated with disease relapse in patients with GCA treated only with glucocorticoids.3,11–13 Identified predictors for treatment failure have included sex,10 clinical features at disease onset (eg, polymyalgia rheumatica (PMR) symptoms, strong systemic inflammatory response and weight loss),3,16,17 certain
comorbidities (eg, diabetes) and increased serum proinflammatory cytokine levels (IL-6 and tumour necrosis factor-α). 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, 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) 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. 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 mg/day 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, 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, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, 36-Item Short Form Survey (SF-36) and EuroQol-5D (EQ-5D) score (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 IQRs, 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 χ² 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 cohort and the primary analysis are published. The 250 patients...
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 5.3; 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=0.0064) 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.

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 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 65.3% 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). Age, race and body mass index were not associated with treatment outcome (tables 3 and 4).

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)     | 76.0 (75.4)     | 74.0 (75.4)          |
| GCA duration, weeks | 43.7 (73.6)   | 41.9 (78.9)     | 42.7 (76.6)          |
| Newly diagnosed, n (%) | 45.0 (47.0) | 66.0 (50.8)     | 511.0 (49.0)         |
| Cranial symptoms only or cranial and PMR symptoms, n (%) | 75.0 (79.8) | 103.0 (79.4) | 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) | 37.5 (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)          |
| PGIA, 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)           |

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) |          |

* Cochrane-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.
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.
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.1 3 7 26 The absence of reliable biomarkers to monitor disease activity3 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,1 14 15 but the identification of a consistent phenotype associated with treatment failure has been elusive. Predictors previously identified include sex,16 clinical features at disease onset (eg, PMR symptoms and significant weight loss),16 17 certain comorbidities (eg, diabetes)18 and increased serum IL-6 levels.19 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 signaling 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,1 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
receiving at a particular time. Stated another way, once predni- 
sone 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 
level to be reached in a patient. Maintaining each patient at a 

logical, therefore, that patients whose PRO scores were impaired 
score for treatment failure during the trial. In contrast, because most 
patients receiving only glucocorticoids during the trial experi-
enced treatment failure, PROs could not discriminate between 
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 collec-
tion 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 | 0.0081 |
| 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, Euro-Qol-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. 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. 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. 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. 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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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
   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

*Imaging 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. |
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). The EQ-5D score ranges from 0 to 1. Lower numbers indicate worse health status.
Table 2 Causes of nonresponse to treatment

| Cause, n (%) | PBO/PDN N=101 | TCZ/PDN N=149 |
|-------------|----------------|---------------|
| Treatment failure |                |               |
|   Refractory disease |       31 (30.7) |   18 (12.1) |
|   Disease relapse |       36 (35.6)† |   26 (17.4)‡ |
| Other |          |               |
|   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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