Risk Factors for Treatment Failure in Patients With Giant Cell Arteritis Treated With Tocilizumab Plus Prednisone Versus Prednisone Alone

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Note: The entire presentation will be made available to qualified providers on medically.roche.com: https://bit.ly/2pxyFfe
Disclosures

• SH Unizony received research funding from F. Hoffmann-La Roche Ltd/Genentech and is a consultant to Kiniksa, Sanofi, and GlaxoSmithKline
• M Bao and J Han are employees of Genentech and own shares in F. Hoffmann-La Roche Ltd
• J Pei and P Sidiropoulos are employees of Genentech
• Y Luder is an employee of and owns shares in F. Hoffmann-La Roche Ltd
• JH Stone has received research funding from F. Hoffmann-La Roche Ltd/Genentech and Xencor and is a consultant to Chugai, F. Hoffmann-La Roche Ltd/Genentech, and Xencor
Until recently, giant cell arteritis (GCA) treatment was limited to lengthy courses of glucocorticoids (GCs)\(^1-4\)
- Between 40% and 80% of patients treated with GCs alone experience ≥1 relapse
- Risk factors for relapse in GC-treated patients are incompletely understood
- GC-toxicity is almost universal in patients with GCA receiving only GCs

The standard of care in GCA is changing with the approval of tocilizumab (TCZ) following the GiACTA study\(^2\)
- However, up to 30% of patients receiving TCZ (+/- GCs) relapse\(^2,5,6\)
- Risk factors for relapse in TCZ-treated patients are unknown

Biomarkers to accurately predict relapse in GCA do not exist

Risk stratification based on clinical predictors may assist in choosing the most appropriate treatment and monitoring strategy for individual patients

Objective

- To identify predictors of treatment failure in patients with GCA receiving TCZ or PBO in combination with prednisone in the GiACTA study
GiACTA Study Design and Primary Results

GiACTA Definitions

**GCA diagnosis** required all of the following:
1. Cranial or PMR clinical manifestations
2. Increased ESR and/or CRP
3. Positive biopsy or cross-sectional imaging

**Flare**: recurrence of signs or symptoms of GCA and/or ESR ≥ 30 mm/hr attributable to GCA that required treatment (e.g., prednisone increase or re-initiation)

**Remission**: absence of flare and normalization of the CRP

**Sustained remission (primary endpoint)**: remission from week 12 to week 52 with adherence to the protocol-defined prednisone taper

CRP, C-reactive protein; QW, every week; Q2W, every 2 weeks.
GiACTA Study Design and Primary Results

**GiACTA Study Design**

- **26-wk prednisone (n=50)**
- **52-wk prednisone (n=50)**
- **26-wk prednisone + TCZ 162 mg QW (n=100)**
- **26-wk prednisone + TCZ 162 mg Q2W (n=50)**

**Primary End Point**

**GiACTA Definitions**

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**Remission:** absence of flare and normalization of the CRP

**Sustained remission (primary endpoint):** remission from week 12 to week 52 with adherence to the protocol-defined prednisone taper

**GiACTA Results**

**Primary analysis**

- **PBO+26:** 14.0%
- **PBO+52:** 17.6%
- **TCZ QW:** 56.0%
- **TCZ Q2W:** 53.1%

- **26-wk prednisone (n=50):**
  - **PBO+26:** 20.0%
  - **PBO+52:** 33.3%
  - **TCZ QW:** 59.0%
  - **TCZ Q2W:** 55.1%

**Sensitivity analysis excluding CRP from remission definition**

CRP, C-reactive protein; QW, every week; Q2W, every 2 weeks.
Methods: Current Analysis

Design

• Secondary analysis of the GiACTA data set to identify predictors of treatment failure
• The TCZ plus prednisone arms (TCZ group) and the PBO plus prednisone arms (PBO group) were combined

Definitions

• **Treatment response** was defined as the achievement and maintenance of clinical remission from week 12 to week 52 while adhering to the protocol prednisone taper
• **Clinical remission** status was adjudicated by the investigators based on the absence of disease activity, defined as GCA signs/symptoms and/or ESR elevation attributable to GCA that required further treatment (eg, rescue prednisone) regardless of CRP levels
• **Treatment failure** was defined as
  – Inability to achieve clinical remission by week 12 (ie, refractory disease) OR
  – Relapse (ie, flare) between weeks 12 and 52 after clinical remission was achieved by week 12

ESR, erythrocyte sedimentation rate.
Methods: Current Analysis (cont)

Predictors
- Patient-related features (eg, demographic)
- Disease-related features (eg, new-onset vs relapsing disease, duration of disease, clinical manifestations, and levels of inflammatory markers)
- Treatment-related features (eg, TCZ vs prednisone treatment, initial prednisone dose)
- Health-related quality of life (HRQOL) patient-reported outcomes (PROs):
  - Patient Global Assessment of Disease Activity (PtGA) score
  - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score
  - 36-Item Short-Form Survey Instrument (SF-36) score
  - EuroQoL-5 (EQ-5D) score

Statistical Methods
- Continuous and categorical variables were compared using t tests and χ² tests, respectively
- Logistic regression was applied for multivariate analyses
Causes of Nonresponse to Treatment

- Overall, 113 patients (45%) experienced treatment response and 111 patients (44%) experienced treatment failure
  - The remaining 26 patients (10%) were nonresponders for reasons other than treatment failure

<table>
<thead>
<tr>
<th>Rates of Treatment Response/Failure Over 52 Weeks, n (%)</th>
<th>PBO Group N=101</th>
<th>TCZ Group N=149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>27 (27)</td>
<td>86 (58)</td>
</tr>
<tr>
<td>Nonresponders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>67 (66)</td>
<td>44 (30)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>7 (7)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Treatment discontinuation because of an adverse event</td>
<td>3 (3)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Nonadherence to prednisone taper</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Study withdrawal before week 52</td>
<td>2 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Miscellaneous(^a)</td>
<td>1 (1)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

\(^a\)Includes protocol violation and protocol noncompliance.
Rates of Treatment Response and Treatment Failure

- Analysis was conducted in patients who met the definitions of treatment response/failure

<table>
<thead>
<tr>
<th>Rates of Treatment Response/Failure Over 52 weeks, n (%)</th>
<th>PBO Group n=94</th>
<th>TCZ Group n=130</th>
<th>p Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response</td>
<td>27 (29)</td>
<td>86 (66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>67 (71)</td>
<td>44 (34)</td>
<td></td>
</tr>
<tr>
<td>Refractory disease</td>
<td>31 (33)</td>
<td>18 (14)</td>
<td></td>
</tr>
<tr>
<td>Disease relapse</td>
<td>36 (38)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26 (20)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on Cochran-Mantel-Haenszel test for comparing the proportion of patients with treatment response between the TCZ and PBO groups adjusted for starting prednisone dose (≤30 vs >30 mg/day).

<sup>b</sup>Based on ESR elevation alone in 8 patients.

<sup>c</sup>Based on ESR elevation alone in 1 patient.
Univariate Analysis: Patient-Related Features

- **Age, race, BMI, sex**

**All Patients**

- Treatment response (n=113): 85.6%
- Treatment failure (n=111): 65.5%

**Treatment Groups**

- TCZ Group response (n=86): 70.9%
- TCZ Group failure (n=44): 84.1%
- PBO Group response (n=27): 48.1%
- PBO Group failure (n=67): 86.6%

BMI, body mass index.

Statistical significance was tested by $\chi^2$ tests. Only significant $p$ values are shown; all other comparisons were not significant ($p>0.05$).
Univariate Analysis: Disease-Related Features

- At diagnosis: scalp tenderness, vision loss, PMR, jaw claudication,
- At study start: new onset vs relapsing disease, disease duration, ESR, CRP

**Jaw Claudication and PMR Symptoms Patients, %**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaw Claudication</td>
<td>p = 0.037</td>
<td>TCZ Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>response (n=86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCZ Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>failure (n=44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PBO Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>response (n=27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PBO Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>failure (n=67)</td>
</tr>
<tr>
<td>PMR Symptoms</td>
<td>p = 0.017</td>
<td>TCZ Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>response (n=86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCZ Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>failure (n=44)</td>
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<td></td>
<td></td>
<td>PBO Group</td>
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<tr>
<td></td>
<td></td>
<td>response (n=27)</td>
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<tr>
<td></td>
<td></td>
<td>PBO Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>failure (n=67)</td>
</tr>
</tbody>
</table>

Statistical significance was tested by Χ² tests. Only significant p values are shown; all other comparisons were not significant (p > 0.05).

PMR, polymyalgia rheumatica.
Univariate Analysis: Treatment-Related Features

- **Prednisone dose at baseline**

  **All Patients**

  - Treatment response (n=113): Baseline Prednisone Dose, mg/day, mean (SD) = 36.0
  - Treatment failure (n=111): Baseline Prednisone Dose, mg/day, mean (SD) = 34.9

  **Treatment Groups**

  - TCZ Group response (n=86): Baseline Prednisone Dose, mg/day, mean (SD) = 36.3
  - TCZ Group failure (n=44): Baseline Prednisone Dose, mg/day, mean (SD) = 34.3
  - PBO Group response (n=27): Baseline Prednisone Dose, mg/day, mean (SD) = 34.8
  - PBO Group failure (n=67): Baseline Prednisone Dose, mg/day, mean (SD) = 35.3

Statistical significance was tested by 2-sample t tests. Comparisons were not significant ($p>0.05$).
Univariate Analysis: PROs (All Patients)

- PtGA, FACIT-Fatigue, SF-36 PCS, SF-36 MCS, EQ-5D

MCS, Mental Component Summary; PCS, Physical Component Summary. Statistical significance was tested by 2 sample t tests.
Univariate Analysis: PROs (Treatment Groups)

- **TCZ Group**: PtGA, FACIT-Fatigue, SF-36 PCS, SF-36 MCS, EQ-5D
- **PBO Group**: PtGA, FACIT-Fatigue, SF-36 PCS, SF-36 MCS, EQ-5D

Statistical significance was tested by 2 sample t-tests. Only significant \( p \) values are shown; all other comparisons were not significant (\( p>0.05 \)).
Odds ratio >1 indicates that the first group has a higher estimated treatment failure rate than its comparator.
Multivariate Analysis Using SF-36 PCS (Treatment Groups)

**PBO Group**

- Baseline SF-36 PCS (per 10 point decrease): 1.56, p-value 0.1508
- Baseline prednisone dose (≤30 mg/day vs >30 mg/day): 1.80, p-value 0.3207
- Jaw claudication (yes vs no): 1.37, p-value 0.6236
- Sex (female vs male): 5.18, p-value 0.0071
- Symptoms of PMR (yes vs no): 2.20, p-value 0.1572
- Duration of GCA (per 1 year decrease): 0.88, p-value 0.6705

**TCZ Group**

- Baseline SF-36 PCS (per 10 point decrease): 1.79, p-value 0.0220
- Baseline prednisone dose (≤30 mg/day vs >30 mg/day): 2.45, p-value 0.0464
- Jaw claudication (yes vs no): 2.30, p-value 0.0603
- Sex (female vs male): 2.36, p-value 0.1108
- Symptoms of PMR (yes vs no): 1.93, p-value 0.1477
- Duration of GCA (per 1 year decrease): 1.25, p-value 0.2066
- Disease onset (relapsing vs new): 1.14, p-value 0.7911

Odds ratio for treatment failure (95% CI)
### Multivariate Analysis: PROs Were Associated With Risk for Treatment Failure

<table>
<thead>
<tr>
<th>PRO</th>
<th>All Patients</th>
<th>TCZ Group</th>
<th>PBO Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>1.8 (1.2, 2.6)</td>
<td>1.8 (1.1, 2.9)</td>
<td>1.6 (0.9, 2.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>FACIT-Fatigue</td>
<td>1.6 (1.2, 2.2)</td>
<td>1.8 (1.2, 2.6)</td>
<td>1.3 (0.8, 2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PtGA</td>
<td>1.2 (1.0, 1.3)</td>
<td>1.3 (1.1, 1.5)</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.028</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>1.3 (1.0, 1.7)</td>
<td>1.3 (1.0, 1.8)</td>
<td>1.2 (0.8, 1.9)</td>
<td>0.040</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>1.2 (1.0, 1.4)</td>
<td>1.2 (1.0, 1.5)</td>
<td>1.0 (0.8, 1.3)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

All PROs were assessed per 10-point decrease except EQ-5D, which was assessed per 0.1-point decrease.
Conclusions

- Patients treated with TCZ had an 84% lower risk for treatment failure than patients treated with prednisone alone.
- Female sex appeared to increase the risk of treatment failure 5-fold in prednisone-only-treated patients but was not a risk factor for treatment failure in TCZ-treated patients.
- Worse baseline HRQOL and patient's perception of disease activity predicted treatment failure in TCZ-treated patients.
- Lower initial prednisone doses were associated with treatment failure in TCZ-treated patients but not in prednisone-only-treated patients.
- This analysis was exploratory and needs confirmation.

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