A Prospective Open-Label Phase Ila Trial of Tocilizumab in the Treatment of Polymyalgia Rheumatica

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Abstract

Objective—Interleukin-6 (IL-6) is a pivotal cytokine in the pathogenesis of polymyalgia rheumatica (PMR), yet the efficacy of IL-6 blockade with tocilizumab (TCZ) for the treatment of PMR is unknown. The aim of this study was to assess the efficacy and safety of TCZ in newly diagnosed PMR.

Methods—In a single-center open-label study, patients with newly diagnosed PMR who had been treated with glucocorticoids (GCs) for <1 month were treated monthly with intravenous (IV) TCZ 8 mg/kg for 1 year, with a rapid tapering of GCs according to standardized protocol. The primary end point was the proportion of patients in relapse-free remission without GC treatment at 6 months. Secondary outcome measures included duration of GC use and cumulative GC dose. Patients were followed up for 15 months.

Results—Ten patients were enrolled in the study. One patient withdrew after 2 months, leaving 9 patients in whom the primary end point was assessed. The primary end point of relapse-free remission without GC treatment at 6 months was achieved by all 9 of these patients. All patients who received TCZ treatment were able to discontinue GCs within 4 months of study entry. The cumulative mean ± SD prednisone dose was 1,085 ± 301 mg and the total duration of GC exposure was 3.9 ± 0.9 months. Remission persisted without relapse, in all 9 patients, throughout the entire 15-month study.

Conclusion—Our findings suggest that TCZ may be an effective, safe, and well-tolerated treatment for newly diagnosed patients with PMR, with a robust steroid-sparing effect.

Polymyalgia rheumatica (PMR) is a systemic inflammatory disease of the elderly, characterized by proximal muscle pain and stiffness accompanied by elevations in levels of inflammatory markers. Glucocorticoids (GCs) are the cornerstone of treatment for PMR, with a characteristic exquisite symptomatic response within days of starting therapy. Despite the effectiveness of GC therapy, relapse is common in PMR, occurring in ~50% of patients.
Moreover, the majority of patients experience some form of therapy-related morbidity (2). Thus, alternative therapeutic strategies for PMR are needed. While the pathogenesis of PMR is not fully understood, interleukin-6 (IL-6) has long been recognized as a crucial inflammatory mediator in disease development and propagation (3).

Similar to IL-6 levels in giant cell arteritis (GCA), a condition related to PMR, IL-6 levels in untreated PMR are elevated in the peripheral blood and fall rapidly after initiation of GC therapy (4). Persistent elevation in IL-6 is associated with relapsing disease and the need for prolonged GC treatment. Plasma IL-6 and soluble IL-6 receptor (IL-6R) concentrations correlate with disease activity, and elevations have been demonstrated to be more sensitive for detection of disease relapse than are elevations in levels of traditional acute-phase reactants (5).

Despite the recognized relationship between IL-6 levels and PMR disease activity, the role of IL-6 blockade in the treatment of PMR is unknown. There are case reports of successful use of tocilizumab (TCZ), the monoclonal antibody targeting the IL-6R, in PMR, though these were generally retrospective experiences, and many of the reported patients had concurrent GCA and a refractory disease course (6–9). The aim of this study was to evaluate, in a prospective clinical trial, the effectiveness of TCZ in patients with newly diagnosed, isolated PMR.

**PATIENTS AND METHODS**

**Study design and subjects**

This was a single-center open-label prospective study. Enrolled patients were treated monthly with intravenous (IV) TCZ 8 mg/kg (supplied by Genentech) for 1 year in conjunction with a tapering of GCs according to a standardized protocol (Supplementary Table 1, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39740/abstract). Following the initial TCZ infusion, daily dosage of GCs was tapered by 2.5 mg every 2 weeks. As such, patients were anticipated to be without GC treatment within 12 weeks of the baseline visit. Patients were assessed clinically and underwent laboratory evaluations every 2 weeks for the first month, and then monthly thereafter for 1 year. The final study visit occurred at month 15, which was 3 months after the final TCZ infusion.

PMR was defined using the Healy criteria (10); on retrospective assessment after enrollment, all patients met the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2012 provisional classification criteria for PMR, without ultrasound assessment (11). Patients were enrolled within 1 month of diagnosis of PMR and had to have initially received ≤20 mg of prednisone daily or its equivalent to be eligible. Those treated daily with GCs at ≥30 mg/day at any time after PMR diagnosis were excluded from the study, as were those who had received GC therapy for >1 month prior to enrollment. Patients with concurrent GCA were not eligible for enrollment, nor were those with an underlying inflammatory arthropathy or connective tissue disease. Patients who were positive for rheumatoid factor and/or cyclic citrullinated peptide antibody were excluded. Those
receiving concurrent or prior treatment with methotrexate (MTX) or other disease-modifying antirheumatic drugs were also excluded.

A cohort of consecutively evaluated patients with newly diagnosed PMR who declined participation in the trial, or failed to meet inclusion criteria, served as a comparator group (Supplementary Table 2, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39740/abstract). These patients were treated contemporaneously with the comparator group by a single rheumatologist with expertise in PMR (RS) and received GCs alone, tapered at the treating physician’s discretion, as is the standard of care in PMR. Analogous definitions of relapse and recurrence were used for these study subjects and the comparator group. This protocol was approved by our institutional review board.

**Efficacy end points**

The primary endpoint was the proportion of patients whose PMR was in relapse-free remission without GC treatment at 6 months. Relapse was defined as the reappearance of signs and symptoms of PMR, accompanied by an increasing erythrocyte sedimentation rate and/or C-reactive protein level attributable to disease activity. Recurrence was similarly defined as the return of PMR symptoms in conjunction with elevations in levels of inflammation markers, occurring >1 month after discontinuation of GC therapy. Secondary end points included the proportion of patients without GC treatment in relapse-free remission at months 12 and 15, time to first relapse, total number of relapses/recurrences, and cumulative GC dose. The PMR Activity Score(12) and Health Assessment Questionnaire Disability Index (13) were assessed at each study visit.

**Safety assessments**

Safety and tolerability of TCZ were also evaluated during the 15-month study period. Adverse events (AEs) were queried, assessed, and recorded at each visit, and laboratory parameters (such as liver enzyme levels, levels of neutrophils, platelets, and lipids) were serially monitored. Any AE occurring between scheduled study visits was assessed and recorded as the investigators were made aware. All AEs were documented, graded with attribution, assessed by study investigators, and reported to an independent drug safety monitoring board.

**Statistical analysis**

Statistical analysis for this pilot study was predominantly descriptive in nature, using means and standard deviations for continuous variables and frequencies or percentages to describe categorical data. Mann-Whitney U and Fisher’s exact tests were used to compare characteristics of the study patients to those in the comparator group.

This was a pilot study with a planned sample size of 10 patients. In the literature, the expected percentage of patients in whom prednisone can be successfully tapered and discontinued without relapse at 6 months is ~50% (14). A sample size of 10 would therefore provide 85% statistical power to detect an additional 35% above the expected 50% remission rate with a P value for statistical significance set at <0.05.
RESULTS

Subjects

Ten patients with newly diagnosed PMR treated with GCs for <4 weeks were enrolled in our study. There was an equal distribution between men and women among study subjects, and the mean ± SD age at PMR diagnosis was 68 ± 8.5 years. These subjects received a mean initial prednisone dose of 16.5± 6.7 mg daily.

Ten consecutively diagnosed patients were identified as the comparator group. Similar to study participants, these patients all met the Healy criteria and the 2012 ACR/EULAR provisional classification criteria for PMR. The patients in this cohort did not differ from study subjects with regard to age, sex, acute-phase reactant levels at diagnosis, or mean initial GC dose (Table 1).

Efficacy assessments

One subject withdrew from the study after the second TCZ infusion due to a mild infusion reaction, leaving 9 subjects in whom the primary end point was assessed. All 9 of the subjects achieved the primary end point of relapse-free remission without GC treatment at 6 months. Moreover, the disease remained in remission throughout the trial in all 9 patients who completed the 15-month trial, including at the last study visit which was 3 months following the final TCZ infusion. No relapses or recurrences were observed in any of the patients who were treated with TCZ. None of the patients experienced any clinical signs or symptoms consistent with recurrent PMR. The mean PMR Activity Score at screening was 5.3 (range 0.5–18.0); this was reduced to 1.8 at 6 months and 0.87 at 15 months.

In the comparator group, none of the patients were in remission without GC treatment by 6 months. Remission or low disease activity was observed in all of these patients at the 6-month time point, but all were still receiving low-dose GCs; 1 patient had a relapse 4 months following PMR diagnosis. Seven relapses in 6 patients in this group were observed over a 12-month period. At 12 months, a relapse rate of 60% was observed in these patients, contrasting sharply to the lack of relapses seen in any of the TCZ-treated subjects (Table 2).

Steroid-sparing effects

All study subjects who completed the trial were able to adhere to the rapid standardized GC taper without the need for resumption of steroids once they had been discontinued. Eight subjects permanently discontinued GCs following the third dose of TCZ, while in the ninth patient, GCs were discontinued following the fourth TCZ infusion. The mean ± SD cumulative prednisone dose that was administered to TCZ-treated patients from the time of PMR diagnosis was 1,085 ± 301 mg. In the comparator group treated with standard-of-care GC monotherapy, the mean cumulative dose from the time of PMR diagnosis was 136% higher than that in the patients treated with TCZ, at 2,562 ± 1,356 mg ($P=0.01$) (Table 2).

The total duration of GC treatment from PMR diagnosis (prior to study enrollment) was 3.9 months in the TCZ-treated subjects. Again, the total duration of GC exposure was
significantly longer in the comparator group, who received GCs for a mean of 14.1 months (P= 0.002).

**Safety**

Twenty-two AEs were observed in patients treated with TCZ (Table 3). One reaction to infusion was observed, leading to discontinuation of the study drug in that subject. The most frequently observed event was upper respiratory tract infection, which occurred in 5 patients but was mild in severity. One subject developed episodic neutropenia following each TCZ dose; week-40 and week-48 TCZ infusions were withheld due to an absolute neutrophil count (ANC) of <1.5. No infections were observed in this patient while the ANC was low, and following the discontinuation of TCZ, the ANC returned to normal. One serious adverse event, deemed not attributable to study medication, was observed in a subject who required hospitalization for a small, nondisplaced sternal fracture following a motor vehicle accident; this subject had normal results on a bone density assessment. No osteoporotic fractures were observed during the course of the study. Due to the retrospective nature of data collection in the comparator group, we were unable to thoroughly assess AEs in this population.

**DISCUSSION**

The treatment of PMR remains clinically challenging due to the fact that the current standard of care is exceptionally effective but has a high degree of morbidity in the elderly patient population. In this phase IIa study, we were able to demonstrate that treatment with TCZ in conjunction with a rapid tapering of GCs was an effective, well-tolerated, and seemingly safe strategy for patients with newly diagnosed PMR.

To our knowledge, our study is the first prospective trial of treatment using TCZ in combination with GCs in patients with newly diagnosed PMR. This study differs from individual case reports and case series of TCZ treatment in PMR previously reported in the literature (9,10), given our use of standardized treatment protocols including a structured tapering of GCs, and our routine clinical and laboratory assessments. Moreover, many of the previous reports of TCZ treatment in PMR include patients with concurrent GCA. Given the rapidity of the steroid taper and the risk of ischemic complications in GCA, we were careful to exclude patients with signs or symptoms of GCA. Devauchelle-Pensec et al recently conducted a prospective study of 20 patients in whom PMR had been diagnosed within 1 year of study entry. Patients were treated with 2 doses of TCZ (8 mg/kg IV every 4 weeks) without GCs, followed by initiation of GC treatment at a tapering dose (15). The authors concluded that TCZ monotherapy was effective in recent-onset PMR. Though the design and duration of TCZ treatment differed from those used in the present study, the congruent findings between these 2 studies may suggest a considerable steroid-sparing benefit of TCZ in PMR.

This study is also the first report of TCZ therapy in patients with newly diagnosed PMR treated concurrently with GCs at a rapidly tapering dose according to standardized protocol. Prior reports have described use of TCZ, with variable effectiveness, in patients whose PMR was refractory to GCs or who were unable to tolerate GC therapy (9,10,11,16). For this pilot, proof-of-concept study, we considered it important to use a population of patients with
isolated PMR and new-onset disease. The lack of any observed flares in TCZ-treated patients over a 15-month period supports the notion that early treatment with TCZ not only enables sparing of GCs, but also may play a role in remission maintenance. Previous studies have suggested that rapid tapering of GCs is associated with an increased risk of relapse in PMR (16); in the present study, despite a very rapid tapering of steroids, no relapses were observed during the 15-month period.

Presently, no other robust steroid-sparing agent for PMR has been identified. MTX has been the most widely studied agent for PMR, with several randomized controlled trials addressing its efficacy (17,18). In a recent systematic literature review of treatment in PMR, the authors concluded that while the reported data are of mixed quality, MTX may be of clinical benefit in newly diagnosed PMR (19). In the largest of these studies (18), Caporali et al found that, with the addition of MTX, the median cumulative prednisone dose at week 76 was 2,100 mg, compared to 2,970 mg in the placebo group; while this difference was statistically significant, the clinical significance is questionable as no differences in steroid-related toxicity were demonstrated. Furthermore, follow-up after 5 years showed no difference in steroid-related side effects between patients treated with MTX and those treated with placebo, with one-third of all subjects requiring >6 years of GC therapy (20).

In contrast, the patients in the present study who were treated with TCZ received a mean cumulative prednisone dose of 1,085 mg. While head-to-head comparisons of different study cohorts are difficult, the magnitude of difference in cumulative steroid burden between the TCZ-treated patients and both the historical MTX-treated patients and the contemporary comparator group suggests an impressive steroid-sparing effect of TCZ. Similarly, the patients treated with TCZ were exposed to an average of <4 months of GC therapy, a marked difference from the mean duration of 2 years of GC treatment often reported in the literature (2). Steroid-related toxicity is overwhelmingly related to cumulative dose; thus, a therapy that allows for rapid discontinuation of GCs offers great potential benefit.

IL-6 is recognized as a pivotal proinflammatory cytokine in PMR. As such, there is solid biologic rationale supporting IL-6 inhibition as a viable treatment to regulate the inflammatory signs and symptoms of the disease. The therapeutic mechanism of action of IL-6 blockade in PMR is not fully understood. In other rheumatic diseases, including GCA, treatment with TCZ has been shown to increase peripheral Treg cells (21). Modification of Treg cell quantity and/or activity may modulate the therapeutic effect of TCZ in PMR, and is a mechanism that can be further explored.

While the open-label nature and small size of this study are obvious limitations, the positive results with no observed relapses/recurrences and a profound steroid-sparing effect in patients treated with TCZ suggest a probable clinical effect. In our study, relapses and recurrences were classified using a standard definition requiring clinical symptoms with accompanying elevations in levels of inflammation markers. Treatment with IL-6 blockade can uncouple inflammation markers from active systemic inflammation; as such, ESR and CRP levels during TCZ treatment may not accurately reflect disease activity. Thus, the lack of elevation in ESR and/or CRP levels observed during TCZ therapy as observed in the current study was not entirely surprising.
However, in conjunction with the persistent normalization of levels of inflammation markers during TCZ treatment, none of our subjects experienced symptoms consistent with active PMR. Though this was not a controlled study, identification of a contemporaneously diagnosed cohort of consecutively diagnosed patients with PMR, treated with the current standard of care, allowed comparison of TCZ-treated patients with a demographically similar cohort. While in this small study no severe TCZ-related AEs were observed, a larger cohort is needed to fully assess the safety of this therapy in PMR, especially as compared to low-dose GC therapy. Additionally, this study was designed for a proof of concept and did not take pharmacoeconomic considerations into account.

In conclusion, this study demonstrated that TCZ is an effective and well-tolerated therapy for newly diagnosed, isolated PMR, with an impressive steroid-sparing effect. A randomized controlled trial is warranted to confirm these favorable results.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**ROLE OF THE STUDY SPONSOR**

Genentech 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 Genentech.

**References**


Table 1
Baseline demographic characteristics of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>TCZ-treated patients (n = 10)</th>
<th>Comparator group (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Age, mean ± SD years</td>
<td>68 ± 8.5</td>
<td>72 ± 10.7</td>
</tr>
<tr>
<td>ESR at diagnosis, mean (range) mm/hour</td>
<td>63.2 (13–116)</td>
<td>62.5 (30–123)</td>
</tr>
<tr>
<td>CRP at diagnosis, mean (range) × ULN</td>
<td>3.8 (1.3–6.0)</td>
<td>9.7 (1.1–22.2)</td>
</tr>
<tr>
<td>Met ACR/EULAR 2012 provisional classification criteria for PMR, without ultrasound, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Initial prednisone dose, mean ± SD mg/day</td>
<td>16.5 ± 6.7</td>
<td>16.5 ± 4.1</td>
</tr>
</tbody>
</table>

*TCZ = tocilizumab; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein (levels provided are elevations above the upper limit of normal [ULN] of the laboratory reference range, as different laboratories have different reference ranges); ACR = American College of Rheumatology; HI LAR = European League Against Rheumatism; PMR = polymyalgia rheumatica.
## Table 2

Remission rates and steroid-sparing effects

<table>
<thead>
<tr>
<th></th>
<th>TCZ-treated patients (n = 9)*</th>
<th>Comparator group (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-free remission at 6 months, no. (%)</td>
<td>9 (100)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relapse at 12 months, no. (%)</td>
<td>0 (0)</td>
<td>6 (60)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cumulative prednisone dose, mean ± SD mg</td>
<td>1,085.3 ± 301.3</td>
<td>2,562.0 ± 1,355.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of prednisone exposure, mean ± SD months</td>
<td>3.9 ± 0.9</td>
<td>14.1 ± 6.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* TCZ = tocilizumab.
### Table 3

Adverse events by type

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>Severity (n)</th>
<th>Relation to study therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infection</td>
<td>5</td>
<td>1 (4), 2 (1)</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia (ANC &lt;1.5)</td>
<td>7</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Elevated total cholesterol</td>
<td>2</td>
<td>1, 2</td>
<td>2, 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rotator cuff tendinitis</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lower back pain</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nondisplaced fracture of sternum</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Knee osteoarthritis</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Trigger finger surgery</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* One adverse event (nondisplaced fracture of sternum) was classified as a serious adverse event. ANC = absolute neutrophil count.

† 1 = mild; 2 = moderate; 3 = severe; 4 = life threatening; 5 = death.

‡ 1 = unrelated; 2 = unlikely, 3 = possibly; 4 = probably; 5 = definite.