A Prospective Open Label Phase IIa Trial of Tocilizumab In the Treatment of Polymyalgia Rheumatica

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Objectives: 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, subjects with newly diagnosed PMR and prior treatment with less than 1 month of glucocorticoids (GCs) were treated with TCZ 8mg/kg IV monthly for one year plus a rapid standardized GC taper. The primary endpoint was the proportion of subjects in relapse-free remission off GCs at 6 months. Secondary outcomes included duration of GC use and cumulative GC dose. Subjects were followed for 15 months.

Results: Ten subjects were enrolled. One subject withdrew after 2 months, leaving 9 subjects in whom primary endpoint was assessed. All 9 of these subjects achieved the primary endpoint of relapse-free remission off GCs at 6 months. All TCZ-treated subjects were able to discontinue GCs within 4 months of study entry. Cumulative prednisone dose was 1085±301mg and total duration of GC exposure was 3.9±0.9mos. All 9 subjects remained in remission without relapse throughout the entire 15 month study.

Conclusions: Our findings suggest TCZ may be an effective, safe and well-tolerated treatment for newly diagnosed PMR with a robust steroid-sparing effect.
Introduction

Polymyalgia rheumatica (PMR) is a systemic inflammatory disease of the elderly characterized by proximal muscle pain and stiffness accompanied by elevations in inflammatory markers. Glucocorticoids (GCs) are the cornerstone of treatment for PMR with a hallmark exquisite symptomatic response within days of starting therapy. Despite the effectiveness of GC therapy, relapses are common in PMR, occurring in approximately 50% of patients.\(^1\) 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 (IL)-6 has long been appreciated as a crucial inflammatory mediator in disease development and propagation.\(^3\) Similar to the related condition, giant cell arteritis (GCA), IL-6 levels are elevated in the peripheral blood of patients with untreated PMR and fall rapidly after initiation of GCs.\(^4\) Persistent elevation in IL-6 is associated with relapsing disease and a prolonged GC requirement. Plasma IL-6 and soluble IL-6 receptor concentrations correlate with disease activity and elevations have been demonstrated to be more sensitive for detection of disease relapse than 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-6 receptor, in PMR, though these were generally retrospective experiences, and many of the reported patients had concurrent GCA and a refractory disease course.\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^9\) The aim of this study was to evaluate the
effectiveness of TCZ in subjects with newly diagnosed isolated PMR in a prospective clinical trial.

Methods

Study Design and Subjects

This was a single center, open-label prospective study. Enrolled subjects were treated with TCZ 8mg/kg IV monthly for 12 months in conjunction with a standardized GC taper (S1). Following the initial TCZ infusion, GCs were tapered by 2.5mg every two weeks. As such, subjects were anticipated to be off of GCs within 12 weeks of the baseline visit. Subjects were assessed clinically and had laboratory evaluations every 2 weeks for the first month and then monthly thereafter for 12 months. The final study visit occurred at month 15, which was three months after the final TCZ infusion.

PMR was defined using the Healy Criteria\textsuperscript{10}; all enrolled subjects also retrospectively met the ACR/EULAR 2012 Provisional Classification Criteria for PMR without ultrasound.\textsuperscript{11} Subjects were enrolled within one month of diagnosis of PMR and had to have received ≤20mg of prednisone daily or its equivalent initially to be eligible. Those treated with GC doses of prednisone 30mg daily or its equivalent at any time after PMR diagnosis were excluded from the study, as were those who had received GC therapy for more than one 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 with a positive rheumatoid factor and/or CCP antibody were excluded. Concurrent or prior treatment with methotrexate (MTX) or other DMARDs was not permitted.
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 (S2). These patients were treated contemporaneously to study subjects 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 when managing these patients and the study subjects.

This protocol was approved by our Institutional Review Board.

**Efficacy Endpoints**

The primary endpoint was the proportion of subjects in relapse-free remission off GCs at 6 months. Relapse was defined as the reappearance of signs and symptoms of PMR accompanied by an increasing sedimentation rate and/or C-reactive protein attributable to disease activity. Recurrence was similarly defined as the return of PMR symptoms in conjunction with elevations in inflammatory markers occurring more than one month after discontinuation of GC therapy. Secondary endpoints included the proportion of subjects off GCs in relapse-free remission at month 12 and 15, time to first relapse, total number of relapses/recurrences and cumulative GC dose. PMR Activity Score (PMR-AS) and Health Assessment Questionnaire Disability Index (HAQ-DI) were assessed at each study visit.

**Safety Assessments**

Safety and tolerability of TCZ was 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, 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 and Fisher’s Exact tests were used to compare characteristics of the study subjects to those in the comparator group.

This was a pilot study with planned sample size of 10 subjects. The expected percentage of patients that can be successfully tapered off prednisone without relapse at 6 months is approximately 50% in the literature. A sample size of 10 would therefore provide 85% power to detect an additional 35% above the expected 50% remission rate, with a p value for statistical significance set at p< 0.05.

Results

Subjects

As planned, 10 subjects with newly diagnosed PMR treated with <4 weeks of GCs were enrolled. There was an equal distribution between men and women among study subjects and the mean age at PMR diagnosis was 68±8.5 years old. These subjects received on average an initial prednisone dose of 16.5±6.7mg daily.
Ten consecutively diagnosed patients were identified as the comparator group. Similar to study participants, these patients all met Healy Criteria and 2012 ACR/EULAR Provisional Classification Criteria for PMR. The patients in this cohort did not differ from study subjects with regard to age, gender, acute phase reactant elevations at diagnosis or mean initial GC dose. (Table 1)

**Efficacy Assessments**

One subject withdrew after the second TCZ infusion due to a mild infusion reaction, leaving nine subjects in whom primary endpoint was assessed. All nine of the subjects achieved the primary endpoint of relapse-free remission off of GCs at 6 months. Moreover, all nine subjects who completed the 15 month trial remained in remission throughout the trial, including at the terminal study visit which was three months following the final TCZ infusion. No relapses or recurrences were observed in any of the study participants who were treated with TCZ. None of the study subjects experienced any clinical signs or symptoms consistent with recurrent PMR. The mean PMR-AS 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 respectively.

In the comparator group, none of the patients were in remission off of GCs by 6 months. All of these patients achieved remission or low disease activity at the 6 month time point, but all remained on low dose GCs; one patient had a relapse 4 months following diagnosis. Seven relapses in six 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 nil relapses seen in the TCZ-treated subjects. (Table 2)
Steroid-sparing effects

All study subjects who completed the trial were able to adhere to the rapid GC taper without the need for resumption of steroids once discontinued. Eight subjects permanently discontinued GCs following the third dose of TCZ, while the ninth subject tapered off GCs following the fourth TCZ infusion. The mean cumulative prednisone dose from the time of PMR diagnosis in TCZ treated subjects was 1085±301mg. In the comparator group treated with standard of care GC monotherapy, the mean cumulative dose from time of PMR diagnosis was 136% higher at 2562±1356mg (p-value 0.01).

Total duration of GC 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 a mean of 14.1 months of GC treatment (p-value 0.002).

Safety:

Twenty-two adverse events were observed in subjects on TCZ (Table 3). One infusion reaction was observed, leading to discontinuation of the study drug in that subject. The most frequently observed events were upper respiratory tract infections, which occurred in five patients and were mild in severity. One subject developed episodic neutropenia following each TCZ dose; this subject had week 40 and week 48 TCZ infusions held due to absolute neutrophil count (ANC) <1.5. No infections were observed in this subject while the ANC was low and following the discontinuation of TCZ, this subject’s ANC returned to normal. One SAE, deemed not attributable to study medication, was observed in a subject who required hospitalization for a small non-displaced sternal fracture following a motor vehicle accident; this subject had a
normal 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, AEs in this population were unable to be thoroughly assessed.

Discussion

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

To our knowledge, ours is the first, prospective protocolized trial of TCZ in combination with GC in newly diagnosed PMR. Standardized treatment protocols, including a structured GC taper, and routine clinical and laboratory assessments differentiate this study from the case reports and series of TCZ use in PMR previously reported in the literature.\(^9,10\) Moreover, many of the prior reports of TCZ in PMR include those with concurrent GCA. Given the rapidity of our steroid taper and the risk of ischemic complications in GCA, we were careful to exclude patients with signs or symptoms of GCA. A recently published prospective study treated 20 subjects diagnosed with PMR within 12 months with three doses of TCZ (8mg/kg IV every 4 weeks) without GCs followed by a tapering dose of GCs, with the authors concluding TCZ monotherapy was effective in recent onset PMR.\(^13\) Though the design and duration of TCZ treatment differed
from the current study, the congruent findings amongst these two studies may suggest an appreciable steroid-sparing benefit of TCZ in PMR.

This is also the first report of TCZ therapy in newly diagnosed PMR treated concurrently with a standardized GC taper. Prior series have described use of TCZ with variable effectiveness in patients refractory to or intolerant of GC therapy or as monotherapy.\textsuperscript{9,10,11,14} For this pilot, proof of concept experience, we felt having a population of patients with isolated PMR and new onset disease was important. The lack of any observed flares in TCZ-treated subjects over a 15 month period does support the notion that early treatment with TCZ not only enables sparing of GCs but may also have a role in remission maintenance. Prior studies have concluded that rapid GC tapering is associated with an increased risk for relapse in PMR\textsuperscript{14}; in the present study, despite a very rapid steroid taper, no relapses were observed during the 15 month study.

Presently, no other robust steroid-sparing agent for PMR has been identified. MTX has been the most widely studied agent for PMR with several RCTs addressing its efficacy.\textsuperscript{15,16} A recent systematic literature review of treatment in PMR concluded that while the quality of these data is mixed, MTX may be of clinical benefit in newly diagnosed PMR.\textsuperscript{17} In the largest of these studies, Caporali et al found that with the addition of MTX, the median cumulative prednisone dose at week 76 was 2100mg compared to 2970mg 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 of after five years showed no difference in steroid-related side effects between MTX and placebo treated patients with one third of all subjects requiring more than six years of GC therapy.\textsuperscript{18}
In contrast, the subjects in the present study treated with TCZ received a mean cumulative prednisone dose of 1085mg. While head-to-head comparisons of different study cohorts are difficult, the magnitude of difference in cumulative steroid burden between the TCZ treated subjects and both the historical MTX treated subjects and the contemporary comparator group, suggests an impressive steroid-sparing effect of TCZ. Similarly, the TCZ treated patients were exposed to an average of less than four months of GC therapy, a marked difference from the two years of treatment often reported in the literature as mean duration of GCs. Steroid related toxicity is overwhelmingly related to cumulative dose; thus, a therapy which allows for rapid discontinuation of GCs offers great potential benefit.

IL-6 is recognized as a pivotal pro-inflammatory cytokine in PMR. As such, there is a solid biologic rationale supporting IL-6 inhibition as a viable treatment to modulate 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 T regulatory cells. Modification of T regulatory 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 TCZ treated subjects suggests a probable clinical effect. In our study, relapses and recurrences were defined using a standard definition requiring clinical symptoms with accompanying elevations in inflammatory markers. Treatment with IL-6 blockade can uncouple inflammatory
markers from active systemic inflammation; as such, ESR and CRP levels during TCZ treatment may not accurately reflect disease activity. Thus, the lack of elevations in ESR and/or CRP observed during TCZ therapy was not entirely surprising. However, in conjunction with the persistent normalization of inflammatory markers during TCZ treatment, none of our subjects experienced symptoms consistent with active PMR. Though this was not a controlled study, the identification of a contemporaneously diagnosed cohort of consecutively diagnosed PMR patients treated with the current standard of care did allow comparison of study subjects with a demographically similar cohort. While in this small study no severe tocilizumab related adverse events were observed, a larger experience 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 as 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.

Acknowledgments

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### Table 1: Baseline Demographics

<table>
<thead>
<tr>
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<th>Subjects</th>
<th>Comparator Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age (yrs), mean±SD</td>
<td>68±8.5</td>
<td>72±10.7</td>
<td>0.44</td>
</tr>
<tr>
<td>Mean ESR at diagnosis, range</td>
<td>63.2 (13-116)</td>
<td>62.5 (30-123)</td>
<td>0.91</td>
</tr>
<tr>
<td>Mean CRP at diagnosis (xULN), range</td>
<td>3.8 (1.3-6.0)</td>
<td>9.7 (1.1-22.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>ACR/EULAR 2012 Provisional Classification Criteria for PMR, without ultrasound (%)</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Initial Prednisone Dose (mg), mean±SD</td>
<td>16.5±6.7</td>
<td>16.5±4.1</td>
<td>0.87</td>
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</tbody>
</table>

ESR = erythrocyte sedimentation rate

CRP = c-reactive protein, levels provided are elevations above the upper limit of normal of the laboratory reference range, as different laboratories had different reference ranges.

### Table 2: Remission Rates and Steroid-Sparing Effects

<table>
<thead>
<tr>
<th></th>
<th>Subjects</th>
<th>Comparator Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-free Remission Rate at 6 months (n)</td>
<td>100 % (9/9)</td>
<td>0 % (0/10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relapse Rate at 12 months (n)</td>
<td>0 % (0/9)</td>
<td>60% (6/10)</td>
<td>0.03</td>
</tr>
</tbody>
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### Table 3: Adverse Events by Type

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number</th>
<th>Severity (n)</th>
<th>Relation to study therapy</th>
<th>Seriousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Infection</td>
<td>5</td>
<td>1 (4), 2 (1)</td>
<td>3</td>
<td>AE</td>
</tr>
</tbody>
</table>

Cumulative Prednisone dose (mg), mean±SD

<p>| | | | | |</p>
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<tbody>
<tr>
<td></td>
<td>1085.3 ± 301.3</td>
<td>2562.0 ± 1355.9</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Duration of Prednisone Exposure (months), mean±SD

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<tbody>
<tr>
<td></td>
<td>3.9 ± 0.9</td>
<td>14.1 ± 6.0</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Condition</td>
<td>Cases</td>
<td>Moderate</td>
<td>Severe</td>
<td>Death</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
<td>----------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>Neutropenia (ANC&lt;1.5)</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Elevated Total Cholesterol</td>
<td>2</td>
<td>1, 2</td>
<td>2, 3</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Infusion Reaction</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Rotator cuff tendonitis</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Light-Headedness</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lower Back Pain</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-displaced fracture of sternum</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
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<tr>
<td>Oral Herpes</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
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<tr>
<td>Osteoarthritis knee</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
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<tr>
<td>Trigger Finger surgery</td>
<td>1</td>
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**Key**

- **Severity**
  - 1 = Mild
  - 2 = Moderate
  - 3 = Severe
  - 4 = Life Threatening
  - 5 = Death

- **Relation to study therapy**
  - 1 = Unrelated
  - 2 = Unlikely
  - 3 = Possibly
  - 4 = Probably
  - 5 = Definite

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Tocilizumab in PMR


