Tocilizumab is effective against polymyalgia rheumatica: experience in 13 intractable cases

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ABSTRACT
Polymyalgia rheumatica (PMR) affects older people, and although glucocorticoids are effective in treating PMR, they frequently result in side effects. Therefore, we conducted a retrospective study to assess the effectiveness and safety of tocilizumab as an alternative to glucocorticoids. We included 13 consecutive patients with PMR (11 women and 2 men; median age, 74 years) diagnosed according to Bird’s criteria and the 2012 European League Against Rheumatism/American College of Rheumatology provisional classification criteria. All patients received tocilizumab infusion (8 mg/kg every 4 weeks) at our institutions, between 2008 and 2014, because of PMR relapses (n=12) or insufficient response to initial prednisolone treatment (n=1), without increasing prednisolone dosage. Seven patients were on methotrexate, and all had one or more glucocorticoid-related comorbidities. Administration of tocilizumab significantly improved inflammation and PMR symptoms such as morning stiffness, as well as the Patient-Pain and Patient-Global Assessment visual analogue scales (p<0.05). Proximal muscle pain disappeared within 8 weeks, on average, and the Health Assessment Questionnaire-Disability Index scores (p=0.098) and concomitant prednisolone doses (p<0.05) decreased at 12 weeks. Severe adverse events were not observed during the mean tocilizumab treatment period of 43.4 weeks. Our findings suggest that tocilizumab is effective and safe for PMR treatment.

INTRODUCTION
Polymyalgia rheumatica (PMR) is the second most common inflammatory rheumatic disease after rheumatoid arthritis,1 and affects older people. Despite their side effects, glucocorticoids are still the only known effective treatment, and low-dose prednisolone is normally sufficient for controlling the disease. However, when PMR recurs during prednisolone tapering, physicians are sometimes reluctant to increase prednisolone doses because of the side effects. Since interleukin 6 has been reported to play an important role in PMR,2 we assessed the effectiveness and safety of tocilizumab as an alternative therapeutic option for intractable PMR.

METHODS
We conducted a retrospective investigation of all consecutive patients with PMR, diagnosed according to Bird’s criteria3 and the 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) provisional classification criteria,4 who were started on tocilizumab between April 2008 and January 2014 at Keio University Hospital or National Tokyo Medical Center. Our study design was approved by each of the institutional review boards. Health Assessment Questionnaire-Disability Index scores and visual analogue scales (VAS) of Patient-Pain, Patient-Global Assessment (GA) and Physician-GA were recorded prospectively.

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RESULTS
Thirteen patients (11 women and 2 men) were included in the study, and all received tocilizumab infusion at a dose of 8 mg/kg every 4 weeks (a lower dose of tocilizumab was not used). At baseline, the patients’ median age and disease duration were 74 years (range 56–87 years) and 8 months (range 1–65 months), respectively. The duration from initiation of glucocorticoid to initiation of tocilizumab was equal to the disease duration of PMR because all patients were started on glucocorticoid at the time of diagnosis. Except for patient 4, who refused prednisolone treatment, all patients had used prednisolone before the initiation of tocilizumab. In all cases, tocilizumab was added because of a relapse of PMR (n=12) or lack of initial response to prednisolone treatment (n=1). At the start of tocilizumab therapy, doses of prednisolone were not increased. Relapses and lack of response were judged by attending physicians, and the choice of treatment was at the physicians’ discretion.

As shown in table 1, at baseline, 12 patients received prednisolone with a median dose of 6 mg/day (range 1–14 mg/day). Seven were on methotrexate with a median dose of 8 mg/week (range 6–12 mg/week), but a further increase in methotrexate doses was not considered because there were concerns related to nausea, liver dysfunction, or cytopenia. Six were not on methotrexate because of liver or renal dysfunction, low body weight, or older age.

All patients had one or more comorbidities, such as osteoporosis (n=11), hypertension (n=7), diabetes mellitus (n=3), dyslipidemia (n=2) or glaucoma (n=1), related to glucocorticoid therapy, during which treatment for these comorbidities was added or strengthened. None had giant cell arteritis (GCA) or any malignancy.

Tocilizumab significantly improved PMR symptoms such as morning stiffness (MS), Patient-Pain and Patient-GA (figure 1A–C). Proximal muscle pain disappeared in 8 weeks (range 4–24 weeks) on average. Median C-reactive protein (CRP) level and erythrocyte sedimentation rate significantly decreased from 2.30 mg/dL (range 0.30–14.72 mg/dL) at baseline to 0.24 mg/dL (range 0.01–2.80 mg/dL) at 4 weeks and from 46 mm/h (range 19–99 mm/h) to 6 mm/h (range 2–46 mm/h), respectively (figure 1D, E). Health Assessment Questionnaire-Disability Index scores decreased from 3.75 (range 0–2.75) at baseline to 0 (range 0–1.75) at 12 weeks (p=0.098). Overall, concomitant prednisolone doses significantly decreased from 6 mg/day (range 0–14 mg/day) at baseline to 1 mg/day (range 0–9 mg/day) at 12 weeks (figure 1F). Prednisolone doses were reduced by 1 mg every month in 12 patients and by 0.5 mg every month in 1 patient. Of 12 patients who used prednisolone at baseline, 7 had discontinued prednisolone by the last follow-up. The median tapering rate of prednisolone over the follow-up period was 1.3 mg/day (range 0–2.5 mg/day) per 4 weeks. VAS of Physician-GA significantly decreased from 36.5 (range 2–93) at baseline to 6.5 (range 0–18) at 4 weeks (p=0.004).

All patients continued to receive tocilizumab treatment for a mean period of 43.4 weeks (range 12–96 weeks). During the observation period, none of the patients discontinued tocilizumab treatment. One patient had a 1-week postponement of tocilizumab infusion at 20 weeks because of phlegmon, which was improved by antibiotics administration; subsequently, tocilizumab infusion was continued. Other complications associated with tocilizumab were thrombocytopenia (n=1), leg oedema and leucopenia (n=1), but these complications were so mild as to require no discontinuation and no reduction of tocilizumab. None of the patients experienced relapses of PMR.

DISCUSSION
To the best of our knowledge, this is the first report of a case series showing significant effectiveness and steroid-sparing effects of tocilizumab for treating relapsed PMR. In addition, tocilizumab was well-tolerated even in elderly patients who had glucocorticoid-related comorbidities.

Several studies have evaluated the efficacy of methotrexate and tumour necrosis factor (TNF) inhibitors, but their efficacy including steroid-sparing effects has been controversial.5–8 Recently, EULAR and ACR published the 2015 recommendations for the management of PMR, in which the use of TNF inhibitors for treatment of PMR was strongly recommended; however, the use of methotrexate was conditionally recommended, particularly in patients at a high risk for relapse and/or prolonged therapy or in patients with a relapse, without significant response to glucocorticoids or experiencing glucocorticoid-related adverse events.9

Hagihara et al first reported a case of PMR in a 71-year-old woman treated with tocilizumab, who had experienced a few relapses with prednisolone (dose 8–10 mg/day) and had experienced exacerbation of diabetes mellitus, hypertension and osteoporosis.10 In this case, 5 monthly infusions of tocilizumab resulted in the resolution of MS and remission of PMR, and after 11 monthly infusions of tocilizumab, the dose of prednisolone could be reduced from 10 to 6 mg/day. Christidis et al next reported the case of a 70-year-old woman with a 7-year history of PMR followed by new onset of GCA. This case exhibited a lack of effectiveness or tolerance to methotrexate, leflunomide and azathioprine; however, within 24 h of the first infusion of tocilizumab, excellent response was obtained with disappearance of pain in the shoulders and pelvic girdle as well as relief of MS.11 Since these two reports, some other reports have also provided favourable results regarding the effectiveness of tocilizumab against PMR with or without GCA.12–15 We also administered tocilizumab to the patients with PMR because they had glucocorticoid-related comorbidities and did not want
| Characteristics of the patients | Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | Mean ±SD |
|--------------------------------|---------|---|---|---|---|---|---|---|---|---|----|----|----|----|----------|
| n=13                           |         |   |   |   |   |   |   |   |   |   |    |    |    |    |          |
| Age, years*                    |         | 56| 59| 65| 65| 66| 71| 74| 76| 80| 83 | 84 | 86 | 87 | 73.2 ±10.4 |
| Sex (female, n %)              |         | F | F | M | F | M | F | F | F | F | F  | F  | F  | F | (84.6) |
| Body weight, kg*               |         | 54| 55| 66| 45| 76| 52| 45| 52| 33| 40 | 45 | 60 | 59 | 52.4 ±10.9 |
| Disease duration, months*      |         | 4.0| 7.0|23.0|16.0|1.0|34.0|4.0|8.0|65.0|2.0 |8.0 |5.5 |18.0 |15.0 ±17.8 |
| Duration of morning stiffness, min* |     | 30| 360|180|1440|180|ND |300|30 |0  |0  |0  |0  |0  |220 ±441 |
| Patient-Pain, VAS (0–100), mm* |         | 54| 83| 25| 55| 31| ND| 34|10 |92 |20 |20 |26 |49 |36.2 ±23.8 |
| Patient-GA, VAS (0–100), mm*   |         | 54| 74| 33| 43| 62| ND| 38|20 |90 |13 |20 |42 |76 |43.7 ±25.3 |
| Physician-GA VAS (0–100), mm*  |         | 38| 76| 7 | 2 | 24| ND| 35|21 |93 |40 |33 |48 |42 |34.5 ±25.4 |
| HAQ-DI*                        |         | 0.375|2.375|0.125|1 |0.625|ND |0.125|0 |2.75|1.25 |0 |0.125|0 |0.73 ±0.95 |
| ESR, mm/h*                     |         | 21| 85| 20| 99| 46| 46| 40|19 |71 |98 |19 |61 |22 |49.7 ±30.4 |
| CRP, mg/dL*                    |         | 1.8| 6.8|0.9|3.4|1.6| 2.8|2.5|0.3|14.7|4.3 |0.8 |2.3 |1.3 |3.34 ±3.83 |
| Previous therapies             |         | PSL, MTX|PSL, MTX|PSL, MTX|PSL, SASP|PSL, MTX|PSL, SASP|PSL, MMZ, MTX|PSL, MTX|PSL, MTX|PSL, MTX|PSL, MTX|PSL, MTX|PSL, PSL|PSL, MTX|
| Number of relapses before TCZ start |     | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |          |
| Reasons for start of TCZ       |         | Relapse|Relapse|Relapse|Relapse|Lack of initial response|Relapse|Relapse|Relapse|Relapse|Relapse|Relapse|Relapse|Relapse|Relapse |
| MTX dose, mg/week*             |         | 6 | 8 | 12 |0 |0 | 0 | 0 |10 |0  |6  |8  |0  |0  |4.5 ±4.5  |
| MTX dose at the last observation, mg/week | | 2 | 2 | 0 | 0 | 8 | 0 | 0 |6  |0  |2  |0  |0  |0  |1.5 ±2.6  |
| PSL dose, mg/day*              |         | 5 | 6 | 8 | 0 |13 | 14 |5 | 5 |2  |7.5 |1  |7  |6  |6.1 ±6.1  |
| Time from TCZ start to disappearance of | | 1 | 0 | 0 | 0 | 5 | 3 | 1 | 0 |0  |0  |0  |0  |0  |0.9 ±1.6  |
| Continued                      |         |   |   |   |   |   |   |   |   |   |   |   |   |   |          |
treatment with increased doses of prednisolone. At 4 weeks, each attending physician judged that tocilizumab was effective in each patient, and went on to reduce the dose of prednisolone, except for patient 4, who was not on prednisolone at baseline. Indeed, symptom-related indices (duration of MS, Patient-Pain VAS and Patient-GA VAS) and inflammatory response were significantly decreased at as early as 4 weeks. Moreover, at 12 weeks, we observed a significant glucocorticoid-sparing effect. No relapse was observed during the study period, and 8 of the 13 patients could discontinue prednisolone by the last follow-up. Therefore, we recommend that tocilizumab be considered, especially for patients with relapsed PMR who have glucocorticoid-related comorbidities and are not able to tolerate methotrexate.

When tocilizumab is initiated for patients with relapsed PMR, we recommend that tocilizumab be added without simultaneously increasing glucocorticoid doses, in order to ascertain whether tocilizumab is effective against the relapsed PMR. During tocilizumab treatment, it is somewhat difficult to recognise relapses of PMR early because inflammatory responses are masked by tocilizumab. When remission of PMR is obtained with tocilizumab, inflammatory response is completely suppressed in most cases (eg, CRP <0.01 mg/dL). On the other hand, when PMR does not remit or is about to relapse during tocilizumab treatment, CRP levels are slightly increased, even though they remain within normal limits. Besides laboratory data, patients’ symptoms and clinical examinations are important in identifying the relapse. As long as remission is maintained with tocilizumab, we may reduce the dose of tocilizumab or lengthen the infusion interval. Because of the lack of consistent evidence, however, it still remains unclear when to start tapering the tocilizumab dose, how to taper it, and when to discontinue it. In the present study, we tapered daily prednisolone by 1.3 mg every 4 weeks on average, which is faster than the suggested tapering rate for prednisone (1 mg decrements per 4 weeks) in the 2015 recommendations by EULAR and ACR.9

We suggest first aiming at discontinuation of glucocorticoids while initiating administration of a standard dosage of tocilizumab in patients with PMR who have glucocorticoid-related comorbid diseases. With tocilizumab, the dose-tapering rate of daily prednisolone may be faster than 1 mg decrements per 4 weeks. Then, after the discontinuation of the glucocorticoid, we suggest that reduced dosage (dose reduction or spacing) of tocilizumab may be considered. Determining the optimal tapering method for tocilizumab is one of our future agendas in patients with PMR, as is the case in patients with rheumatoid arthritis.

Despite these positive findings, our study does have some limitations that need to be mentioned. First, our study was retrospective in nature and did not have a control group. Future randomised controlled
prospective studies are warranted to demonstrate the efficacy and safety of tocilizumab against PMR. The efficacy and safety of tocilizumab in patients with PMR are currently being investigated in two randomised controlled trials (NCT01396317, NCT01713842 (TENOR study)). The results from these phase II studies are awaited with interest. Next, PMR-activity score was not available in our study because the data on elevation of the upper limbs were missing. Moreover, our study population may be slightly skewed because the proportion of women (84.6%) in our study was higher than that in other studies (range 66.6–80.0%).

In conclusion, our study suggests that tocilizumab treatment is effective and safe in patients with PMR who have glucocorticoid-related comorbidities. Tocilizumab may be an alternative therapeutic option for intractable PMR.

Contributors KI collected data, participated in the design of the study, analysed the data, performed the statistical analysis, evaluated the results and drafted the manuscript. HK collected data, participated in the design of the study, analysed the data and helped to draft the manuscript. MU participated in the design of the study, evaluated the results and helped to draft the manuscript. TT participated in the design of the study, analysed the data, performed the statistical analysis, evaluated the results and helped to draft the manuscript. All the authors read and approved the final manuscript.

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