Corticosteroid-free treatment of tocilizumab monotherapy for microscopic polyangiitis: a single-arm, single-center, clinical trial

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Abstract
Objectives: To assess the efficacy of tocilizumab (TCZ) monotherapy for the remission induction of microscopic polyangiitis (MPA) in a prospective single-arm, single-center, cohort, pilot study.
Methods: Eligible patients were aged between 20 and 80 years and were newly diagnosed with MPA according to Watts’ classification algorithm. Seven patients received 8 mg/kg of intravenous TCZ fortnightly for the first 2 months (5 courses), and monthly for the next 10 months (10 courses). One year after TCZ monotherapy, the patients were followed-up without any treatment. The protocol did not permit the use corticosteroids or any other immunosuppressants. Complete remission (CR) was defined as the Birmingham Vasculitis Activity Score of 0 at two consecutive visits made at least a month apart.
Results: CR was achieved in two of six patients (33.3%) at 6 months and three patients (50.0%) at 12 months. Two patients were withdrawn: one because of inefficacy at 6 weeks and the other because of flare at 6 months. One patient voluntarily withdrew after CR at 3 months. Four patients (66.7%) could be kept drug-free after 1 year of TCZ without relapse for 6–15 months at the last visit.
Conclusion: TCZ monotherapy may be an alternative treatment strategy in some patients with MPA.

Introduction

Similar to granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA) is a systemic, necrotizing, and small-vessel vasculitis associated with circulating antineutrophil cytoplasmic antibodies (ANCAs) and is thus called ANCA-associated vasculitis (AAV) [1]. The treatment of MPA and GPA is based on the stage of the disease and its severity, and both corticosteroids (CS) and cyclophosphamide (CYC) have been the main agents for standard remission induction therapy in generalized and/or severe disease [2–4]. However, CS increase the risk of developing potentially serious mid- and long-term side effects caused by infection, diabetes, osteoporosis, and osteonecrosis. Also, CYC is associated with infertility, cytopenia, infection, bladder injury, and cancer [5,6]. Rheumatologists, nephrologists, and other clinicians involved in the management of AAV have been searching for equally effective but less toxic treatment regimens [7,8]. Recently, it was reported that the remission rate of rituximab (RTX)-based regimens was not inferior to that of standard intravenous CYC for AAV [9,10]; therefore, RTX is emerging as the standard therapy to avoid adverse drug reactions of CYC or to treat patients who are refractory to CYC. However, the RTX regimen in the above-mentioned trials was not associated with any reduction in severe adverse events, including infections, during induction therapy [9,10], which is probably because of the use of high dosages of CS [7], although RTX by itself does not appear to increase the risk of infection [11,12]. In addition, RTX appears to require concomitant administration of CS, at least for induction therapy, and reducing CS might lead to relapses during induction and maintenance treatment with other immunosuppressants including CYC [13,14]. Thus, a CS- and CYC-free treatment strategy would be required for AAV patients to avoid adverse drug reactions.

Recently, we reported a case of successful treatment of AAV complicated by rheumatoid arthritis (RA) using tocilizumab (TCZ) without the use of CS and CYC [15], and several reports have suggested that TCZ is a potential treatment for AAV as well as large-vessel vasculitis [16–18]. TCZ is a humanized anti-interleukin (IL)-6 receptor monoclonal antibody [19] and a highly effective therapeutic agent for RA, juvenile idiopathic arthritis (JIA), and Castleman’s disease [20]. Furthermore, a large amount of case reports and case series revealed that TCZ can be an effective therapy for adult-onset Still’s disease (AOSD), inflammatory amyloidosis, relapsing polychondritis, remitting seronegative symmetrical synovitis with pitting edema-syndrome, systemic lupus erythematosus, interstitial lung disease (ILD), giant cell arteritis, polymyalgia rheumatica, and Takayasu arteritis [21]. The use of concomitant CS for RA is a significant risk factor for developing serious infection during TCZ treatment [22]. TCZ has strong anti-inflammatory properties and might be an alternative to CS for treating AAV based on our case report [15]. The aim of the present study is to conduct a prospective single-arm, single-center, cohort, pilot study on the efficacy of TCZ monotherapy for AAV, especially in MPA patients, for the first time.
Methods
Study design and patients
This is a single-arm, single-center, clinical trial conducted in Saitama Medical Center, Saitama Medical University. Eligible patients were aged 20–80 years and were newly diagnosed with MPA according to Watts’ classification [23]. All patients provided written informed consent. The trial received ethical approval from the institutional review board of Saitama Medical Center, Saitama Medical University, and was registered with the UMIN clinical trials registry (UMIN000011242). This study was performed observing the guidelines stipulated by the World Medical Declaration of Helsinki and the Ethical Guidelines for Clinical Research in Japan revised in 2008. The exclusion criteria of this study were those of the Japan College of Rheumatology 2009 guidelines for the use of TCZ on RA [24]. All patients were subscribed to a clinical research insurance covering serious drug-related adverse events or death. If a patient’s condition deteriorated or organ damage was progressing, the patient was immediately withdrawn from this study, and we initiated conventional treatment using CS including pulsed methylprednisolone, and CYC or RTX according to the patients’ condition.

Treatment
The patients received intravenous 8 mg/kg of TCZ fortnightly for the first 2 months (five courses) according to the treatment strategy for JIA [25]. Over the next 10 months, the patients received intravenous 8 mg/kg of TCZ monthly (10 courses) according to the treatment strategy for RA [24] (Supplementary Figure 1). One year after TCZ monotherapy (a total of 15 courses), the patients were followed-up without any treatment for the next 1 year. To alleviate or eliminate the side effects of TCZ, dose reduction and/or interval elongation were allowed according to discretion of an attending physician. The protocol prohibited the use of CS and other immunosuppressants, such as CYC and RTX during the study.

Assessments
The Birmingham Vasculitis Activity Score (BVAS) [26] was used for the evaluation of vasculitis disease activity (scores ranging from 0 to 63, with higher scores indicating a more active disease). Complete remission (CR) and partial response (PR) were assessed to evaluate the efficacy of TCZ monotherapy. CR was defined as BVAS of 0 at 2 consecutive visits made at least 1 month apart, and PR was defined as a 50% reduction of BVAS from the baseline [27]. The vasculitis damage index (VDI) [28] was also evaluated. A major relapse should be defined as the recurrence or a new onset of a potentially organ function-compromising or life-threatening disease that cannot be treated with an increase of CS alone and requires further escalation of immunosuppressive treatment. All other relapses should be classified as minor relapses [29]. Myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA)s and proteinase-3-antineutrophil cytoplasmic antibodies (PR3-ANCAs) were tested by a chemiluminescent [29]. Myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA)s and proteinase-3-antineutrophil cytoplasmic antibodies (PR3-ANCAs) were tested by a chemiluminescent

Endpoint and adverse events
The primary outcomes included the rate of CR/PR and improvement of major clinical signs and symptoms at 12 months, and the relapse rate after withdrawal of TCZ at 24 months. Serious adverse events and adverse drug reactions until 12 months were also recorded.

Statistical analysis
Values are expressed as means ± standard deviation (SD). All analyses were performed with the use of JMP® 12 (SAS Institute Inc., Cary, NC).

Results
Patients
Between October 2013 and March 2015, a total of seven patients were enrolled in the study. All patients were Japanese and were treated at the Saitama Medical Center, Saitama Medical University. Table 1 shows the baseline demographics and clinical characteristics of the enrolled patients. The patients were numbered as patient nos. 1, 2, 3, 4, 5, 6, and 7 in order of their enrollment into this study. An interferon-gamma release test for tuberculosis was positive for patient nos. 1 and 5, so we prescribed isoniazid for the treatment of latent tuberculosis according to the available guidelines [24].

Disease type and organ involvement
All patients fulfilled the inclusion criteria of AAV according to 2007 Watts’ classification algorithm, but none fulfilled the criteria for GPA and EGPA. All patients had renal lesions that were defined by the presence of biopsy-proven vasculitis or active urine sediments according to the established algorithm [23]. Six patients except for patient no. 7 had biopsy-proven fibrinoid necrosis and/or cellular/fibrocellular crescents in the glomeruli or necrotizing arteritis in the interlobular artery. Patient no. 5 was first classified as having unclassifiable vasculitis with MPO-ANCA positivity before the renal biopsy because no active urine sediments were observed. However, the renal biopsy revealed that 1/36 glomeruli showed fibrinoid necrosis in the glomerular capillaries, which was revealed by deeply slicing the biopsy specimen, even in the absence of urine protein, hematuria, and cell casts. Patient nos. 2 and 3 did not have any glomerular lesions, such as fibrinoid necrosis or cellular/fibrocellular crescents, but only had necrotizing arteritis and tubulitis, although the histopathologic classification of ANCA-associated glomerulonephritis is based on glomerular lesions [30]. Immunofluorescence and electron microscopy revealed no immune or electron-dense deposits in any patients. No patient had alveolar hemorrhage. The types of ILD observed in the enrolled patients except for patient no. 7 included combined pulmonary fibrosis and emphysema, non-specific interstitial pneumonia, or usual interstitial pneumonia according to radiographic findings. Sensory peripheral neuropathy defined by nerve conduction velocity and subjective symptoms was seen in all patients except for nos. 2 and 4. Motor neuron disorders were not observed. Skin disorders due to vasculitis were seen in two patients (nos. 1 and 7). Patient no. 1 had livedo reticularis, and patient no. 7 had multiple severe skin ulcers and purpura, which revealed leukocytoclastic vasculitis on skin biopsy; she also had colonic ulcer probably due to vasculitis.

Patient’s disposition
Figure 1 shows the patient’s disposition. Patient no. 2 achieved CR and missed his fifth infusion of TCZ at 2 months based on his own will. However, as shown in Figure 2(a) and (c), the serum CRP level of patient no. 2 increased at 3 months, and after that he re-visited our hospital at 6 months with no treatment during 3 months due to active MPA with BVAS of 7. Patient no. 6 newly
Table 1. Patient baseline demographics and clinical characteristics.

| No. | Age | Sex | Disease duration (months) | Disease type | Organ involvement | MPO-ANCA (U/ml) | CRP (mg/dl) | Cr (mg/dl) | UP (g/day) | BVAS | Renal class | Necrotizing arteritis* | ILD | 2009 FFS | Complications | PMH |
|-----|-----|-----|--------------------------|-------------|------------------|-----------------|--------------|-----------|------------|-------|--------|---------------------|------|---------|----------------|-----|
| 1   | 63  | M   | 5.3                      | Generalized | N, R, P, D       | >300            | 0.3          | 1.79      | 0.62       | 23    | Sclerotic | –                   | CPFE (NSIP) | 3       | IGRA+, Osteoporosis, vertebral body fracture | Gastric ulcer, Prostate cancer |
| 2   | 79  | M   | 1.4                      | Early systemic | R, P          | 71.4            | 9.1          | 1.45      | 0.71       | 15    | Unclassified | +                   | CPFE (NSIP) | 3       | Osteoporosis | None |
| 3   | 67  | M   | 3.3                      | Early systemic | N, R, P       | 165.0           | 7.2          | 0.75      | 0.17       | 12    | Unclassified | +                   | NSIP | 3       | None | None |
| 4   | 79  | M   | 6.2                      | Generalized | R, P           | >300            | 0.1          | 1.66      | 0.81       | 17    | Mixed    | –                   | CPFE (UIP) | 3       | Diabetes mellitus | None |
| 5   | 77  | M   | 2.0                      | Early systemic | N, R, P       | 125.0           | 13.6         | 0.79      | <0.1       | 9     | Focal    | +                   | UIP | 3       | Diabetic retinopathy | None |
| 6   | 66  | F   | 7.3                      | Early systemic | N, R, P       | 104.0           | 12.0         | 0.54      | 0.16       | 13    | Mixed    | –                   | NSIP | 3       | IGRA+, IPMN Systemic sclerosis | None |
| 7   | 58  | F   | 5.8                      | Generalized | N, R, D, G     | 51.2            | 4.9         | 1.34      | 26         | Not done | Not done | None | None | None | None |
| Average | 69.9 ± 8.5 | M:F = 5:2 | 4.5 ± 2.2 | Early systemic:4 Generalized:3 | N:5, R:7, P:6, D:2, G:1 | 159.5±102.7 | 6.7±5.3 | 1.15±0.49 | 0.54±0.47 | 15.6±7.0 | Mixed:2, Sclerotic:1, Focal:1, Unclassified:2 | n = 3 | NSIP:4, UIP:2, CPFE:3 | None | None |

BVAS, Birmingham Vasculitis Activity Score; Cr, serum creatinine; CRP, C-reactive protein; CPFE, combined pulmonary fibrosis and emphysema; D, dermal involvement; FFS, five factor score; G, gastric involvement; IGRA, interferon-gamma release assay; ILD, interstitial lung disease; IPMN, intraductal papillary mucinous neoplasm; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; N, peripheral nerve; NSIP, non-specific interstitial pneumonia; P, pulmonary involvement; PMH, past medical history; R, renal involvement; UIP, usual interstitial pneumonia; UP, urine protein.

*Necrotizing arteritis indicates fibrinoid necrosis in the interlobular artery on renal biopsy.
Figure 1. Patient’s disposition during TCZ monotherapy. CR, complete remission.

Figure 2. Changes in clinical parameters during TCZ monotherapy. Patient no. 2 lost his data at 2 months. (a) BVAS, (b) MPO-ANCA (U/ml), (c) CRP (mg/dl), (d) serum creatinine (mg/dl) and (e) UPCR (g/gCr). BVAS, Birmingham vasculitis activity score; Cr, serum creatinine; CRP, C-reactive protein; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; UPCR, urine protein/creatinine ratio.
developed sensory neuritis at 3 months; however, the other clinical signs and symptoms had been alleviated. Then, the glomerulonephritis of patient no. 6 deteriorated at 6 months, and a re-biopsy of the kidney revealed a change from mixed class to crescentic class glomerulonephritis. Therefore, patient no. 6 was withdrawn from the study and received pulsed methylprednisolone and RTX. In patient no. 7, TCZ monotherapy was ineffective for multiple persistent skin ulcers and colonic ulcer, although she met the definition of PR at one month. There were no cases of withdrawal due to adverse events.

Efficacy

Overall outcomes are displayed in Table 2. CR was achieved in two of six patients (33.3%) at 6 months and three (50.0%) at 12 months. CR or PR at 1 month was observed in six of the seven patients (85.7%); after that, however, three patients were withdrawn (nos. 2, 6 and 7). Therefore, CR or PR in four of six patients (66.7%) was observed, respectively, at 6 and 12 months. Figure 2 shows the changes in clinical disease activity and renal function. The improvement of BVAS (Figure 2a) and MPO-ANCAs (Figure 2b) was seen at 6 months in all but two patients (nos. 2 and 6), and improvement of CRP levels (Figure 2c) was seen in all patients within one month. Three patients could be kept in remission without TCZ, and one patient was kept drug-free without relapse for 6–15 months at the last visit. Patient no. 4 failed to achieve CR because of persistent hematuria without proteinuria and any exacerbation of renal impairment. VDI of all cases remained 1 due to pulmonary fibrosis and cataract.

Organ damage

Serum creatinine levels (normal range: male, 0.4–1.1 mg/dl; female, 0.3–1.0 mg/dl) (Figure 2d) at 6 and 12 months improved in two patients (nos. 1 and 4) and remained normal in two patients (nos. 3 and 5). Meanwhile, serum creatinine levels were exacerbated in two patients (nos. 6 and 7). The spot urine protein/creatinine ratio (UPCR) (Figure 2e) improved in all patients except for nos. 6 and 7.

In five cases of ILD (except no. 2), no apparent exacerbation of radiographic findings or respiratory function test (forced vital capacity and diffusing capacity of the lung for carbon monoxide) was observed during TCZ treatment (Supplementary Figure 2a–k and 3). The exacerbation of nerve conduction velocity and subjective symptoms during TCZ therapy was observed only in two patients (nos. 6 and 7).

Livedo reticularis due to vasculitis was alleviated in patient no. 1; meanwhile, multiple skin ulcers and colonic ulcer due to vasculitis did not improve in patient no. 7.

Safety

Table 2 shows the adverse events and the adverse drug reactions recorded in this study, such as bacterial pneumonia, pneumothorax (patient no. 4), bronchitis, and elevated total bilirubin levels (patient no. 5). Administration was discontinued for 2 weeks in the case of bacterial pneumonia and for 3 weeks in the case of bronchitis according to the protocol. Doses of TCZ were not changed after these adverse events. The patients with pneumothorax and elevated total bilirubin levels were followed-up without any treatment. There was no serious adverse event or drug reaction leading to hospitalization.

Discussion

To our knowledge, this is the first clinical trial of the humanized anti-IL-6 receptor monoclonal antibody, TCZ, and all CS-free treatments in MPA patients. In some cases, in this study, CS and CYC could be safely avoided during the treatment of MPA with TCZ monotherapy. In general, most MPA patients are relatively old [31] and usually have multiple comorbidities such as osteoporosis, diabetes mellitus, and hypertension, which are usually exacerbated due to CS. For lupus nephritis, which has mainly been treated with CS, the RITUXILUP trial has recently shown the possibility of avoiding daily oral CS for the first time in the treatment history [32]. In addition, we reported two cases with AOSD who had been successfully treated with TCZ monotherapy without CS [33]. In the future, all CS-free regimens or regimens involving a rapid reduction of CS dosage to lower the total dosage of CS administered should be evaluated for other autoimmune diseases.

Inflammatory cytokines and chemokines may have a role in the pathogenesis of MPA; in particular, some reports have shown an association with IL-6 [16,34–36]. Moreover, TCZ has the ability to decrease serum MPO-ANCA titers in this trial, and there is a report that IL-6-mediated signaling is involved in the production of MPO-ANCAs in SCG/Kj mice as well [37]. The production of CRP in hepatocytes is mediated by the classic IL-6 signaling pathway [20]. CRP is induced by the overproduction of IL-6, which means that TCZ is effective for CRP-positive MPA. However, two cases in the present study, patient nos. 1 and 4 had pathologically proven MPA despite negative CRP levels at baseline, and both of them were successfully treated with 12 months of TCZ monotherapy. From these two cases, a negative CRP level does not appear to suggest the inefficacy of TCZ in MPA.

The reason why TCZ showed insufficient efficacy for patient nos. 6 and 7 is unclear. Even after two infusions of TCZ, their serum CRP levels were still 1.1 and 0.4 mg/dl (normal range, 0–0.3 mg/dl), respectively. The baseline levels of soluble IL-6 receptor (sIL-6R) predict clinical remission in RA patients treated with TCZ [38], so their sIL-6R levels might be higher than those of responders. Another study suggested that genetic variation in IL-6R aided in predicting the outcome of TCZ therapy in RA patients [39]. We therefore need to compare cytokine profiles, including sIL-6R, between non-responders and responders using TCZ in AAV patients in future studies. In addition, it was reported that gene expression between non-responders and responders using TCZ in RA patients was different and that the gene expression of type I interferon response genes (IFI6, MX2, and OASL) and that MT1G might predict therapeutic responses [40]. Therefore, differences in gene expression between non-responders and responders in trials using TCZ for the treatment of AAV patients might be present in patients with MPA like RA.

It was intriguing that four of six patients (66.7%) could be maintained drug-free after the cessation of TCZ for 6–15 months until the last visit. This may be purely coincidental, but it may also be a consequence of blocking of the IL-6R and IL-6-mediated signaling system. IL-6 regulates the differentiation of naïve CD4+ helper T cells into effector subsets. IL-6, together with TGF-β, preferentially induces the differentiation of naïve CD4+ helper T cells to Th17 cells, which produce the inflammatory cytokine IL-17, but IL-6 inhibits the TGF-β-induced differentiation of these cells to regulatory T cells (Treg) [20]. TCZ affected proportions of circulating Treg cells, B cells, and monocytes, and Treg levels are increased in RA patients during TCZ treatment [41]. If such mechanisms are also present in AAV patients, the proportion of immune cells changed by TCZ might be continued following TCZ infusion.

From the above issues, this TCZ monotherapy in patients with MPA may lead to not only the avoidance of adverse drug reactions of CS and CYC but also drug-free remission after this treatment. However, this therapy may be inadequate for inducing remission...
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Table 2. Overall outcome of this study.

| No. | BVAS | Outcome at the last visit | VDI at 12M | VDI at the last visit | BVAS | Outcome at the last visit | VDI at 12M | VDI at the last visit |
|-----|------|---------------------------|------------|----------------------|------|---------------------------|------------|----------------------|
| 1   | CR   | CR                         | No data    | 1                    | CR   | CR                        | No data    | 1                    |
| 2   | PR   | PR                         | CR         | 1                   | PR   | PR                        | CR         | 1                   |
| 3   | PR   | PR                         | CR         | 1                   | PR   | PR                        | CR         | 1                   |
| 4   | PR   | PR                         | CR         | 1                   | PR   | PR                        | CR         | 1                   |
| 5   | PR   | PR                         | CR         | 1                   | PR   | PR                        | CR         | 1                   |
| 6   | CR   | CR                         | No data    | 1                    | CR   | CR                        | No data    | 1                    |
| 7   | PR   | PR                         | CR         | 1                   | PR   | PR                        | CR         | 1                   |
|     | Rate | CR or PR, 66.7%            | CR or PR, 66.7% | CR or PR, 66.7% | CR or PR, 66.7% | CR or PR, 66.7% | CR or PR, 66.7% | CR or PR, 66.7% |

BVAS, Birmingham vasculitis activity score; CR, complete remission; IVCYC, intravenous cyclophosphamide; M, months; mPSL, methylprednisolone; PR, partial response; PSL, prednisolone; RTX, rituximab; TCZ, tocilizumab.

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Supplementary material available online