Novel treatment strategy of polymyalgia rheumatica targeting drug-free remission

Sirs,

Polymyalgia rheumatica (PMR) develops mainly in the elderly population and disturbs physical function. The low-dose glucocorticoids (GCs) is the standard treatment for PMR (1). However, the achievement of drug-free remission has been challenging because of the high rate of relapse especially in the first year after onset, resulting in increment of cumulative GCs dose that caused in poor treatment outcomes (2). Herein, we report three cases with refractory PMR and one with newly-diagnosed PMR, achieving drug-free remission after short-term of GCs and TCZ therapy.

All four patients met the 2012 provisional classification criteria for PMR at the diagnosis (Table I). Relapse occurred in patient 1–3 under GC monotherapy with or without immunosuppressive drugs. Patient 1 had aseptic necrosis developed on the left femoral head after 1.5 years of GCs monotherapy. Azathioprine or tacrolimus were intolerable and ineffective in patient 1. Patient 4 was newly diagnosed and 15 mg/day of prednisolone was started.

In these patients, 8 mg/kg of monthly TCZ was administered concomitantly with 8–15 mg of prednisolone as the treatment for the relapse in patient 1 to 3. Patient 4 received 162 mg of subcutaneous TCZ injection biweekly following 1 week of GCs therapy. The treatment led to immediate amelioration of clinical signs and symptoms within a month, and GCs was successfully withdrawn within 2 to 7 months. Interestingly, treatment with TCZ was able to be stopped in 3 months after discontinuation of GCs, and relapse-free was maintained for 1.5, 2, 1, and 0.5 years after TCZ discontinuation in the cases 1 to 4, respectively.

None of our patients experienced severe adverse effects (SAE) with GC and TCZ therapy.

Regarding the effectiveness of TCZ against PMR in the case series (3), efficacy of TCZ monotherapy was shown in an open-label clinical study of newly-diagnosed PMR, while improvement of clinical signs and symptoms was slower and weaker than the GCs monotherapy (4). The present cases showed that the concomitant use of GCs with TCZ revealed immediate amelioration of clinical signs and symptoms, which is consistent with a previous open-label study (5). The novel message of the present cases was that discontinuation of TCZ followed by long-term relapse-free remission could be achieved with short-term intensive combination therapy of TCZ and GCs. On the other hand, a prospective observational study showed that TCZ was not required to achieve drug-free remission at two years after one-year TCZ monotherapy (6). Our findings support the short-term initial intensive GCs treatment might be effective to achieve prompt drug-free remission with TCZ.

The use of TCZ for elderly patients has several concerns, namely the safety and cost-effectiveness. Aging is a risk factor of serious infection in rheumatoid arthritis (7), while the cost-effectiveness of TCZ was confirmed (8). Shorter duration of TCZ and lower cumulative dose of GCs would be ideal in terms of safety and cost-effectiveness.

We have to admit the relatively low disease activity and the small number of our patients as our limitations. Prompt diagnosis and early intervention was the reason for relatively low disease activity in our patients, but some may argue this by pointing out the selection bias of our study. The efficacy and safety of short-term combination therapy of TCZ and GCs should be confirmed by a randomised controlled trial with a larger number of patients.

The ultimate goal of treatment against PMR is to abrogate disease activity without relapse, while avoiding the drug-associated adverse events. We suggest that the concomitant short-term administration of TCZ with GCs therapy may promote the achievement of drug-free remission in patients with PMR.

Table I. Effectiveness of the concomitant short-term administration of TCZ with GCs therapy.

Case	Patient 1 67 years, relapse	Patient 2 70 years, relapse	Patient 3 82 years, relapse	Patient 4 72 years, newly-onset
Sex	Female	Male	Male	Male
Disease duration (month)	21	4	6	1
Number of relapses Immunosuppressive agents (ever used)	2 Azathioprine, Tacrolimus	1 -	2 -	None -
Clinical signs and symptoms at administration of TCZ	Unable to walk and EUL below girdle	Neck and girdle pain, morning stiffness	Back pain, morning stiffness	EUL up to shoulder, morning stiffness
CRP at administration of TCZ (mg/dl)	1.0	0.6	0.7	0.8
PMR-AS (at administration of TCZ)	8.0	3.6	3.7	2.8
Treatment regimen of the concomitant therapy	PSL 15mg+ 8mg/kg of TCZ-IV, monthly	PSL 8mg+ 8mg/kg of TCZ-IV monthly	PSL 10mg+ 8mg/kg of TCZ-IV monthly	PSL 15mg+ 162mg of TCZ-SC biweekly
Disappearance of clinical signs and symptoms after concomitant therapy (months)	2	1	1	1
The dosage of PSL after 1 months (mg)	12.5	6	7	10
The dosage of PSL after 3 months (mg)	7.5	2	4	0
The dosage of PSL after 6 months (mg)	0	0	0	0
Duration of GCs treatment after concomitant therapy (months)	6	4	5	2
Duration of treatment with TCZ (months)	11	5	6	4
Duration of relapse-free after discontinuation of TCZ (years)	1.5	2	1	0.5
TCZ associated AE	-	-	-	-
Cumulative dose of PSL after concomitant therapy (mg)	1575	600	750	570

EUL: elevate the upper limbs, PMR-AS: polymyalgia rheumatica-activity score), PSL: prednisolone, TCZ: tocilizumab, IV: intravenous infusion, SC: subcutaneous injection NA: not assessed, AE: adverse events.

Letters to the Editors

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