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Case Report

Remission of Glucocorticoid-Resistant Polymyalgia Rheumatica achieved with Tocilizumab: 2 Case Reports

Introduction

Polymyalgia rheumatica (PMR) is an idiopathic inflammatory disease characterized by pain and stiffness around the shoulders, neck and hips. IL-6 is an important cytokine in the pathogenesis of the disease. Although glucocorticoids (GC) are the current basic treatment, approximately 50% of patients may experience relapses during treatment. There have been case reports of resistant patients treated with Tocilizumab (TCZ), but as there has been insufficient evidence, the 2015 EULAR-ACR did not include TCZ treatment in the PMR recommendations. Two cases of GC-resistant PMR cases where remission was obtained with TCZ treatment are presented in this paper.

Case 1

A 60-year old female patient presented with complaints which had started 3 years previously of morning stiffness lasting for 2 hours and pain in the neck and shoulder girdle. There was no headache, impaired vision or claudication in the jaw. The patient had a history of diabetes mellitus and hypertension. In the physical examination there was seen to be restricted active movements of the shoulders. There was no reduction in temporal sensitivity or temporal pulse. Arthritis and lymphadenopathy were not determined. The laboratory test results were as follows; erythrocyte sedimentation rate (ESR): 79 mm/hr, C- reactive protein (CRP): 13 mg/dl, antinuclear antibody (ANA): negative, rheumatoid factor (RF): negative, and anti-cyclic citrulline protein (Anti-CCP): negative. Treatment was started of 15mg/day prednisolone, but as the clinical and laboratory response was low, in the 4th week 15mg/week methotrexate (MTX) was added. A sufficient clinical response was not obtained with the addition of MTX, so it was accepted that the patient was both GC and MTX-resistant and a 4week IV infusion of 8mg/kg TCZ was started. The prednisolone was gradually reduced and terminated. During follow-up the complaints recovered and acute phase reactants returned to normal. During 13 months of TCZ mono therapy, the patient has had no complaints and no TCZ-related side-effects have been observed.

Case 2

A 77-year old female patient presented with complaints which had started 3 years previously of morning stiffness lasting for 1 hour and pain in the shoulder and hip girdle. There was no headache, no vision-related symptoms or claudication in the jaw. The patient had a history of bronchial asthma. Clinically, there was seen to be restricted active movements of the shoulders and hips. There was no reduction in temporal sensitivity or temporal pulse and no arthritis or lymphadenopathy were determined. In the laboratory test results the following were determined; ESR: 23 mm/hr, CRP: 1.7 mg/dl, ANA: negative, RF: negative, and Anti-CCP: negative. Treatment was started of 15mg/day prednisolone, but as no response was obtained, 10mg/week MTX was added in the 4th week. As the complaints had not recovered, the prednisolone was gradually reduced and terminated. The MTX treatment was also terminated. A 4-week IV infusion of 8mg/kg TCZ was started. After 3 doses of TCZ as mono therapy, neutropenia developed (neutrophil: 600/mm3) so the treatment was terminated. However, in this period, the complaints of the patient had significantly reduced and acute phase reactants had returned to normal. Follow-up has been ongoing for approximately 2 years with no medication.

Discussion

Glucocorticoids remain the basic treatment for PMR. Side-effects related to GCs, such as diabetes, hypertension and osteoporosis are important, especially in the elderly. Previous studies have shown that approximately 65% of patients experience at least one major side effect of GCs [1,2]. Of drugs other than GC that are used in PMR treatment, only the effect of MTX has been proven [3,4,5]. MTX at a dose of 7.5-10 mg/week can be added to the treatment for females with ESR≥ 40 mm/hr, those with peripheral arthritis, those who have developed side-effects with GC and those who have experienced relapse. In both the cases presented in this paper, MTX was used in addition to GC. However, as there was no recovery of the patient's symptoms in either case, the MTX treatment was terminated. In the 2015 EULAR-ACR PMR recommendations,

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the use of anti-TNF drugs is not strongly recommended [4]. In a study by Hutchings et al., a partial or poor response was reported at the rate of 55% for 3-week GC treatment [6]. IL-6 is known to be an important cytokine in the pathogenesis of PMR. The IL-6 level in patients with active PMR has been found to be significantly higher compared to healthy control groups in previous studies and it has been determined that the IL-6 level decreases with GC treatment [7-14]. The IL-6 level of patients during a relapse has also been determined to be significantly higher than that of patients in remission [15]. In resistant cases with elevated IL-6, there is greater occurrence of relapse and GC resistance. Elevation in plasma IL-6 and soluble IL-6 receptor levels is more sensitive for relapse than elevated acute phase reactants [16]. Female gender, advanced age and elevated ESR and CRP are risk factors for relapse/recurrence and prolonged GC treatment [17]. In an analysis by Cimmino et al., in patients started on treatment of 12.5mg/day prednisolone, the only factor determined as an indicator of a good response to GCs was low body weight [18]. In the current Case no 1, the patient was 85kg and thus the low response to GCs was consistent with findings in literature.

TCZ, which is an IL-6 receptor monoclonal antibody, has been reported to be of benefit to resistant PMR patients with concomitant giant cell arteritis (GCA) [16]. However, as there has not yet been sufficient evidence, TCZ treatment was not included in the 2015 EULAR-ACR recommendations for PMR treatment [4]. In a study by Devauchelle et al., 4 weeks of mono therapy of 8mg/kg IV TCZ was applied to 20 PMR patients and in the 12th week the PMR activity score (PMR-AS) of all the patients was <10 and in 85% of the patients, very low disease activity was determined (PMR-AS <7). Those patients were administered 0.150.30 mg/kg/day for 12-24 weeks, depending on the PMR-AS. In 4 patient's leukopenia developed to a level which necessitated reducing the dose or terminating the drug. No major side-effects were seen. Significant recoveries were determined on positron emission tomography (PET), but the effects of TCZ at the tissue level are not well known [19]. The response given to TCZ is slow, with only 45% of patients achieving low disease activity in the 4th week. In a study of 125 PMR patients, it was reported that a full response to GCs was obtained in 71% of patients at the end of the 4th week [19,20]. Although TCZ is an effective treatment option for PMR, it should be evaluated as a secondary treatment option for patients who are resistant to GC, have recurrence and/or GC toxicity, because there may be serious side-effects and the drug is expensive. TCZ should be considered as mono therapy and first treatment option in the very elderly with a high risk of fracture and in patients with comorbidities which are significant in terms of side-effects of GCs. In both Case 1 and Case 2 presented here, GC treatment was tapered and terminated, then TCZ was used as mono therapy. Remission was obtained in both cases and no relapse or recurrence was observed after the administration of TCZ. There was no requirement for GC. The advantage of TCZ is the GC reducing effect but care must be taken in respect of side-effects such as leukopenia and infection. In Case no 2, neutropenia developed. The TCZ treatment was terminated. With support from further research, it can be considered that combined use of TCZ at a dose of 4mg/kg with low-dose GCs could provide both a rapid effect and reduce the risk of side-effects [20]. Izumi et al., reported a series of 13 patients diagnosed with PMR who started TCZ at a mean age of 74 years. The TCZ was started because of relapse in 12 patients and a low initial response to prednisolone in 1 case. An infusion of TCZ 8mg/kg was started and at the end of 8 weeks, the complaints had significantly decreased. The prednisolone doses were gradually tapered to termination.

In daily practice, IL-6 level is not examined. However, in the future it could be used in clinical practice as a prognostic indicator and guidance. TCZ should be considered in PMR treatment in cases of non-response or contra-indications to GCs or relapse, taking the benefit harm balance into consideration.

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