CASE REPORT AND LITERATURE REVIEW

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A TRIANGLE: RHEUMATOID ARTHRITIS, MYASTHENIA GRAVIS AND ANTI-TNF. GOOD NEWS OR BAD NEWS? LONG -TERM FOLLOW-UP: CASE REPORT AND REVIEW OF LITERATURE

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies. Inhibitors of tumor necrosis factor (TNF)-alpha are widely used for treating RA. However, prolonged use of these agents has been associated with induction some autoimmune disease. Here, we have shown that anti-TNF drugs used in long-term follow-up of two patients diagnosed with both RA and myasthenia gravis, are safely.

Keywords: Rheumatoid arthritis, myasthenia gravis, tumor necrosis factor

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies (particularly to rheumatoid factor and citrullinated peptide) (1). Tumor necrosis factor (TNF) is a proinflammatory cytokine that plays a role in the pathogenesis of many chronic inflammatory autoimmune diseases, especially in RA. Anti-TNF-alpha agents inhibit the proinflammatory effect and reduce the activity of the disease. As a result with this mechanism improves the RA and many other autoimmune disease symptoms (2). Despite these important clinical benefits, long-term use of biological agents such as TNF Alpha inhibitors may trigger antibody development, and various autoimmune events may occur (3). Some demyelinating diseases are activated during the use of biological agents. Although biological agents are contraindicated in demyelinating diseases of the central nervous system, such as multiple sclerosis, there is no more information and advice about the relationship between anti TNF-alpha agents and prognosis of myasthenia gravis (MG), an autoimmune disease affecting the neuromuscular junction. Here, we reported long-term follow-up results of two patients diagnosed with both RA and MG, with similar cases in the literature.

CASE REPORT

Case-1

A 58-year-old woman was admitted to the neurology clinic in 1999 with asymmetric ptosis, weakness in both arms and legs, inability to hold the neck, and speech disorders. In her neurological examination, it was determined that tetraparesis, bilateral asymmetric ptosis, binocular diplopia after physical effort, and nasone speech, able to count to 20 before his voice became inaudible. An electromyography (EMG) study

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was performed from the extraocular and extremity muscles, and a significant decrement was detected. The patient was diagnosed with MG and given intravenous immunoglobulin (IVIG). Pyridostigmine 3x1 and methylprednisolone 10 mg/day were started. The patient underwent chest computerized tomography (CT) for possible thymoma, but no thymoma was detected. The patient undergoes annual routine checks for MG. After 9 years, pain and swelling of the hand and wrist joints started. On the rheumatological examination, symmetrical arthritis was detected. Her blood tests revealed rheumatoid factor (195 IU), elevated sedimentation (72 mm/h), C-reactive protein (45 mg/L) and anticyclic citrullinated peptide antibodies (450 RU/mL). According to the current clinic features and values, the patient was diagnosed with RA and treatment was started as methotrexate 15 mg/week, sulfosalazin 2 g/day, and hydroxychloroquine 400 mg/day. Although joint complaints decreased but not fully healed, therefore etanercept was added to the current treatment after 3 months. Adalimumab was added after the patient, who had been in remission for about 3 years, showed an exacerbation after her complaints. The patient is still under adalimumab treatment and has been in remission for 7 years. While the patient was taking available biological agents for RA, no myasthenic crisis or increase in the MG clinic was observed. He received only once IVIG treatment at the time of diagnosis. Until now, the dose of oral pyridostigmine did not exceed 3 pieces/day. Oral steroid doses were consistently taken at 5 or 10 mg doses. Routine checks for MG were performed on average twice a year for 20 years. During this period, he did not have any complaints such as increased extremity weakness, binocular diplopia, fall in the eyelid, swallowing and speech impairment, and breathing difficulties.

Case-2

A 35-year-old woman was admitted to the neurology clinic in 2009 with unilateral ptosisand weakness of both arms and legs. In her neurological examination, it was determined that tetraparesis, asymmetric ptosis, and diplopia after physical effort, able to count to 15 before his voice became inaudible, nason speech and increase ptosis after the eye strain test. An EMG study was performed from the extraocular and extremity muscles, and a significant decrement was detected. The patient was diagnosed with MG and given IVIG. Oral pyridostigmine 5x1 and methylprednisolone 10 mg/day were started. The patient underwent a chest CT for a possible thymoma. The chest CT scan showed a neoplastic anterior mediastinal mass, compatible with timoma. The patient underwent thymectomy surgery. The clinic of MG is stable with the current oral treatmen; after 3 years, pain and swelling in the hand joints started. Her blood tests revealed rheumatoid factor (340 IU), elevated sedimentation (65 mm/h), C-reactive protein (93 mg/L) and anticyclic citrullinated peptide antibodies (210 RU/mL). According to the current clinic features and laboratory values, the patient was diagnosed with RA and treatment was started as methotrexate 15 mg/week, hydroxychloroquine 200 mg/day, and prednisolone 5 mg/day. After his complaints were not exceeded, approximately 5 months later, adalimumab was added to the treatment. Methotrexate was stopped because it was nauseous. Sulfosalazin was added instead. The patient is still under treatment as adalimumab 40 mg every 15 days, hydroxychloroquine 200 mg/day, and methylprednisolone 2 mg/day. Due to MG, pyridostigmine takes 4x1 in maintenance therapy. No myasthenic crisis and worsening in the MG clinic have been observed for 11 years.

DISCUSSION

Here, we have shown that anti-TNF agents are safe in two patients with RA and MG, and that they do not cause any exacerbation related to MG.

Despite these important clinical benefits, long-term use of biological agents such as TNF-alpha inhibitors, may trigger antibody development and relieve various autoimmune events (3). Although there are many studies showing that anti TNF-alpha agents predispose to demyelinating diseases in the central nervous system, there is not much data on the relationship between antibody-mediated autoimmune diseases such as MG. MG is an autoimmune disease of the neuromuscular junction caused by antibodies that attack the components of the postsynaptic membrane and disrupt neuromuscular conduction. As a result leads to weakening and fatigue of the skeletal muscle (4). Because autoimmune diseases of the neuromuscular junction are antibody mediated, B lymphocytes play an important role in this process. B lymphocytes need T lymphocytes to become sensitive to target antigens at the neuromuscular junction and to produce high -affinity antibodies. Therefore, both humoral and cellular immune systems must interact mutually for developing autoimmune neuromuscular junction diseases (5). Gradolatto et al. (6) showed that immunoregulation defects observed in MG patients were caused by both Treg and Tconv cell disorders and was central to many proinflammatory processes, including TNF-alpha. Additionally, it was revealed by the polymerase chain reaction study that TNF-alpha plays a role in the pathogenesis of MG disease (6). Duan et al. (7) revealed that IL-6 and TNF-alpha are associated with MG pathogenesis and immunoregulation. Additionally, this study demonstrated that IL-32 induced TNF-alpha, which is central to experimental autoimmune MG induction and development (7). In a prospective pilot study by

Tüzün et al. (8) reported improvement in steroid-dependent MG patients after treatment with etanercept. In this study, it was found that anti-TNF agents increased the level of circulating immune complexes without changing plasma anti-ach receptor antibody levels (8). In line with the findings that support the role of TNF-alpha in the etiopathogenesis of MG, there are a limited number of studies showing that anti-TNF agents may be a treatment alternative in MG. In contrast, there are a few rare studies with case studies showing that anti-TNF agents can trigger MG. In a case reported by Fee et al. (9), they presented a patient who developed MG while receiving etanercept treatment and who developed MG symptoms related to etanercept as the first case in the literature. However, etanercept came to the fore as an alternative agent recommended for treating MG in the coming years (9). In another case report showing that TNF-alpha blockers can trigger MG, methotrexate, and cyclosporine were started in a patient diagnosed with psoriatic arthritis. After a while, these agents were discontinued and etanercept was applied for 10 years. Then, ustekinumab was given. Thymoma and myasthenic symptoms appeared 6 months after ustekinumab was started. After these agents were discontinued and methotrexate and prednisolone were replaced, myasthenic symptoms improved (10). There are potential side effects of long-term immunosuppressant agents in MG. It has been supported by a limited number of studies that TNF-alpha inhibitors can be preferred instead of these immunosuppressant drugs in MG (11). However, it has been reported in several cases that TNF-alpha blockers used in various autoimmune chronic inflammatory diseases can trigger another autoimmune disease, such as MG (12,13) (Table 1).

Table 1. The features of cases associated with MG during the use of biological agents for rheumatological disease

	Nicocia et al. (10)	**Fee et al. (9)**	**Angelucci et al. (12)**	**Pelachas et al. (13)**	**Bixio et al. (11)**	**Our case-1**	**Our case-2**
Age/gender	50/M	66/M	68/F	42/F	1. Case: 48/M 2. Case: 55/F 3. Case: 54/F	58/F	35/F
The type of rheumatological disease and disease duration	PSA 15 years	RA Unknown	RA comorbidity: Crohn's disease, uveitis	RA 2 years	1. Case: RA 2. Case: RA 3. Case: RA	RA 11years	RA 8 years
Presence of MG before rheumatological disease and duration	No	No	No	No	1. Case: No 2. Case: No 1. Case: Yes, 22 years	Yes 20 years	Yes 11 years
Type of autoantibody and serum levels	Unspecified	Unspecified	Unspecified	Anti-CCP: -RF:+	1. Case: Anti-CCP: + RF: + 2. Case: Anti-CCP: + RF: - 1. Case: Anti-CCP: + RF: +	Anti-CCP: + RF: +	Anti-CCP: + RF: +
The thymus	Thymus hyperplasia	Normal	Normal	Normal	1. Case: Normal 2. Case: Normal 3. Case: Thymus hyperplasia and thymectomy	Normal	Thymus hyperplasia
Myasthenic symptoms or MG crisis during biological agent treatment	Yes (4 years after beginning etanercept treatment)	Yes (occured during etanercept treatment)	None	Yes (18 month after beginning adalimumab treatment)	1. Case: None 2. Case: None 3. Case: None	None	None
Possible trigger agent for MG	Etanercept	Etanercept	None	Adalimumab	1. Case: None 2. Case: None 3. Case: None	None	None
Biological and other agent treatment for rheumatological disease	MTX cyclosporine etanercept ustekinumab	Etanercept	Infliximab and adalimumab	MTX prednisone adalimumab	1. Case: MTX, UPA 2. Case: LEF, UPA 3. Case: GC, HCQ, CTZ-peg	Etanercept: 3 years Adalimumab: 7 years	Adalimumab: 7 years

MG: Myasthenia gravis, RA: Rheumatoid arthritis, CCP: Cyclic citrullinated peptide, MTX: Methotrexate, UPA: Upadacitinib, LEF: Lymphoid enhancer factor-1, RF: Rheumatoid factors, HCQ: Hydroxychloroquine, CTZ: Certolizumab

CONCLUSION

In both cases we presented, our patients were followed for more than 10 years with the diagnosis of RA. The diagnosis of MG was initially present in both of our patients. Our patients use etanercept and adalimumab because of RA. In both of our patients, the MG clinic has been stable for many years, and no myasthenic crisis was encountered in this process. In both of our patients, there was no clinical deterioration in MG due to the TNF-alpha blockers used for RA. Our cases show that TNF-alpha blockers are safe in MG disease, even if they are used for many years. Because the number of our cases is few, more comprehensive and extensive studies are needed to prove the accuracy of this hypothesis. Additionally, our patients were given agents such as low -dose steroids and methotrexate in addition to TNF-alpha blockers for RA. The use of these agents may be related to the stable clinic of MG clinics in our patients. As a result, we can say that TNF-alpha blockers can be used safely in MG, which is based on 2 cases we have followed for many years. In addition to the limited number of studies demonstrating that TNF-alpha blockers may be included in the treatment protocol in the long term in MG in the following years, there is a need for more comprehensive and controlled studies involving the larger population in this regard. In addition to the limited number of studies showing that TNF-alpha blockers may be included in the treatment protocol in the long term in MG in the following years, the opposite has been shown in some cases where these agents trigger MG. Therefore, controlled studies involving a wider and larger population are needed.

1- Anti-TNF agents can be used safely in the long term in patients that have additional diagnosis such as myasthenia gravis.

2- Anti-TNF agents do not significantly worsen symptoms of myasthenia gravis disease in the long term.

3- There are very few studies investigating the effects of the use of anti-TNF agents on the course of myasthenia gravis disease.

Ethics

Informed Consent: Patient consent has been obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K., F.A., H.E.Ö., B.K., Design: E.K., F.A., H.E.Ö., B.K., Data Collection or Processing: E.K., F.A., H.E.Ö., B.K., Analysis or Interpretation: E.K., F.A., H.E.Ö., B.K., Literature Search: E.K., F.A., H.E.Ö., B.K., Writing: E.K., F.A., H.E.Ö., B.K.

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