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RESEARCH ARTICLE

Tumor Necrosis Factor-alpha Inhibitors: Can They Induce an Idiopathic Inflammatory Demyelinating Disease in the Central Nervous System?

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Abstract

Objective: Tumor necrosis factor-α (TNF-α) inhibitors are used extensively in the treatment of inflammatory diseases in rheumatology, ophthalmology, and neurology. Despite their therapeutic benefits, inflammatory demyelinating lesions or relapses have been observed following TNF-α inhibitor use.

Materials and Methods: Of the 295 patients who were screened, 258 were included in the study. The demographic characteristics, diagnoses, accompanying diseases, TNF-α agent(s) used, drug usage, and exposure times were recorded. The neurological symptoms and clinical visits were also documented.

Results: The study included 142 females and 116 males, with a mean age of 43.82±11.81 years. Twenty-eight patients used three or more TNF-α inhibitors for an average of 72.42 months. Fifty-eight patients used two TNF-α inhibitors for 55.7 months, and 172 patients used a single TNF-α inhibitor for 45.27 months. During the follow-up, a brain magnetic resonance imaging (MRI) was obtained in 63 patients. Most of these MRIs showed asymptomatic lesions that met one Barkhof criteria and scored one on Fazekas scale for deep and periventricular white matter lesions. One patient with idiopathic uveitis exhibited symptoms of a demyelinating lesion.

Conclusion: TNF-α inhibitors appear to be mostly safe with regards to the induction of inflammatory demyelinating diseases/lesions. However, patients with idiopathic uveitis may be predisposed to developing or presenting with inflammatory/demyelinating lesions of the central nervous system.

Keywords: TNF-α, multiple sclerosis, rheumatology, uveitis, demyelinating disease

Introduction

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine produced by both innate and acquired immune cells, including macrophages and lymphocytes (1). It can also be secreted by microglia, neurons, and astrocytes in the central nervous system (CNS) (1). In pathological conditions, TNF-α can cause tissue injury. In acute phases of multiple sclerosis (MS), elevated TNF-α expression has been observed within demyelinating plaques (2). However, TNF-α inhibitors may reportedly worsen MS relapses despite positive outcomes in experimental autoimmune encephalomyelitis models (3,4). Recent case reports have suggested a link between TNF-α inhibitors and symptoms indicative of MS or demyelinating disease (5). Thus, in this study, we aimed to evaluate patients treated with TNF-α inhibitors for neurological and demyelinating disease symptoms during their follow-up.

Materials and Methods

In this retrospective study, patients being treated with TNF-α inhibitor for a rheumatological disease, who had visited the rheumatology department for follow-up, were included in the study. The demographic characteristics of all the patients were collected. Among the included participants, patients who were admitted under the neurology department before the study

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period and who underwent imaging any time point during the follow-up period were screened. Patients who developed uveitis were analyzed separately. Details regarding exposure duration and number of TNF-α agents were collected.

The lesions detected on magnetic resonance imaging (MRI) were evaluated using the radiologically isolated syndrome (RIS) criteria because they were asymptomatic. The proposed diagnostic criteria of RIS are as follows:

A. The presence of incidentally identified white matter anomalies that meet the following MRI criteria:

1) Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum; 2) T2 hyperintensities measuring ≥3 mm and fulfilling the Barkhof criteria (at least three out of four) for dissemination in space (DIS); 3) anomalies not exhibiting a clear vascular pattern; and 4) structural neuroimaging abnormalities that cannot be explained by another disease process.

B. No history of clinical symptom remittance that is consistent with neurological dysfunction.

C. The MRI anomalies do not account for clinically apparent impairments in social, occupational, or general functioning.

D. The MRI anomalies are not the direct physiological effects of substances (recreational drugs or toxic substances) or a medical condition.

E. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter changes that lack clear involvement of the corpus callosum.

F. The CNS MRI anomalies are not better accounted for by another disease process (6,7).

The MRI lesions were also evaluated using the Barkhof criteria as follows: a) ≥9 lesion on T2-weighted images, exhibiting hyperintensity or ≥1 gadolinium enhancing; b) ≥1 infratentorial lesion; c) ≥1 juxtacortical lesion; and d) ≥4 periventricular lesions.

The sites and severity of the lesion were categorized using the Fazekas scale for white matter lesions as follows: (a) periventricular white matter (PVWM), graded as 0= absent, 1= "caps" or pencil-thin lining, 2= smooth "halo", and 3= irregular periventricular signal extending into the deep white matter; and b) deep white matter (DWM), graded as 0= absent, 1= punctate foci, 2= beginning confluence, and 3= large confluent areas (8). The mean number of lesions, dissemination in time (DIT), and DIS (periventricular, cortical/juxtacortical, infratentorial, and spinal) were noted. During the follow-up the presence of any of the following characteristics were noted: ovoid lesion, lesions perpendicular to the ventricle, and black hole lesions or lesion with gadolinium enhancement.

This study was approved by the Ethics Committee of University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital (approval number: 514/194/8, date: 27.01.2021). Written informed consent was obtained from all the participants.

Statistical Analysis

All statistical analyses were performed using SPSS (version 21.0). The frequencies and percentages, means and standard deviations, or medians with minimum and maximum values were calculated for the data. Additional analyses were not required.

Results

Demographic Characteristics

Out of the 295 screened patients, 258 were included. The study included 142 females (55.08%) and 116 males (44.96%). The mean age of the study participants was 43.82±11.81 years (females, 46.16±11.93 years; males, 40.96±11.05 years). The diagnoses included in the study were ankylosing spondylitis (n=150), rheumatoid arthritis (n=82), Behçet's disease (n=8), psoriatic arthritis (n=17), and enteropathic arthritis (n=1) (Table 1).

Of the 258 included patients, 130 had a systemic disease. Eighty-four patients had vascular risk factors such as hypertension (n=67; hypertension alone, n=27), diabetes mellitus (n=37), coronary artery disease (n=15), hyperlipidemia (n=13), dysrhythmia, (n=5), and pulmonary embolism (n=3). The other patients had non-vascular diseases such as asthma (n=14), thyroid dysfunction (n=10), kidney stones (n=5), Hepatitis B virus infection (n=5), uveitis (n=13), and epilepsy (n=4).

TNF-α Exposure Duration

Of the 295 patients, 173 were prescribed a single TNF-α inhibitor for an average of 45.75±32.91 months. The drugs used were etanercept (n=43), adalimumab (n=59), infliximab (n=14), certolizumab (n=29), and golimumab (n=28). Fifty-seven patients were prescribed two TNF-α inhibitors for an average of 56.35±47.07 months. Twenty-eight patients were prescribed three or more TNF-α inhibitors for an average of 72.42±30.35 months (Table 2).

Table 1. Demographic characteristics of the study patients

Demographic characteristics	
Age (mean ± SD; year)	43.82±11.81
Female (n, %) Male (n, %)	142 (55.08%) 116 (44.96%)
Ankylosing spondylitis (n, %)	150 (58.13%)
Rheumatoid arthritis (n, %)	82 (31.78%)
Behçet's disease (n, %)	7 (2.71%)
Psoriatic arthritis (n, %)	17 (6.589%)
Enteropathic arthritis (n, %)	1 (0.387%)
Idiopathic uveitis	1 (0.387%)

SD: Standard deviation

Neurological Symptoms and Neurology Outpatient Visits

During their rheumatological follow-up, 81 patients visited the neurology outpatient clinic for the following symptoms: headache (n=42), vertigo (n=12; four with a headache, one with a transient ischemic attack, and two with seizures), extrapyramidal symptoms (restless legs syndrome; n=4), facial numbness and ataxia (n=1), and hemiparesis (n=1). The other 21 patients had neck pain, back pain, and disc herniation/bulging without any specific neurological findings.

Imaging Findings

An MRI was obtained in 63 patients. Of these, 12 were brain and cervical spine scans, 19 were cervical spine scans alone, six were diffusion-weighted images, and one was a hypophysis scan. A cranial computerized tomography (CT) was obtained in 29 patients.

Of the 19 patients with brain MRIs, 15 exhibited abnormalities on their MRI. An extraparenchymal subdural hematoma, arterial infarction, and bilateral frontal encephalomalasia was observed in one patient each.

Table 2. Mean duration of exposure to TNF-α inhibitor

TNF-α inhibitor mean exposure	Time (month)
Single agent (n=173)	
Etanercept (n=43)	44.09±35
Adalimumab (n=59)	52.98±35.56
Infliximab (n=14)	59.2±40.17
Sertolizumab (n=29)	28.96±19.27
Golimumab (n=28)	42.17±24.41
Two different agents (n=57)	56.35±47.07
>3 agents (n=28)	72.42±30.35
All patients (n=258)	45.75±32.91

TNF-α: Tumor necrosis factor-alpha

The 15 patients with an MRI lesion were grouped according to the Barkhof criteria, Fazekas DWM and PVWML locations, and lesion type (Table 3). The mean lesion count was eight. According to the MRI, the lesions were localized as follows: periventricular (n=10), cortical/juxtacortical (n=8), new T2 lesion (N/A), ovoid pattern (n=0), perpendicular to the ventricle (n=0), corpus callosum (n=2), black hole (n=2), >3 mm lesion (n=10), gadolinium enhancement (n=1), and infratentorial/spinal cord (n=0). According to the Barkhof criteria of lesions scored 0 (n=6), 1 (n=4), 2 (n=3), and >3 (n=2).

Most of the patients had periventricular and juxtacortical lesions that scored 0 and 1 on the Barkhof scale. Furthermore, most of them scored 1 and 2 on Fazekas scale, indicating an ischemic origin rather than a demyelinating disease. One patient was meeting MS DIT criteria according to the McDonald's 2017 criteria.

Analysis of Patients with Uveitis

Thirteen patients were treated with TNF-α inhibitors developed uveitis with or without a rheumatological disease. Of the 13 patients, 8 (61.53%) were female and 5 (38.46%) were male. The mean age of the patients in this group was 44.69±11.22 years.

The rheumatological diagnoses of the patients in this group were ankylosing spondylitis (n=6), Behçet's disease (n=3), rheumatoid arthritis (n=3), and idiopathic (n=1). The neurological signs/symptoms observed in this group were headache (n=3), extrapyramidal movement disorder (n=1), cerebral venous thrombosis (n=1), radiculopathy (n=1), ataxia with sensorial dysfunction (n=1), and right hemiparesis with decreased consciousness (n=1).

The mean treatment time in patients who were prescribed a single TNF-α inhibitor (adalimumab, n=6; infliximab, n=3; and etanercept, n=1) was 41.7±31.56 months. The mean treatment time in the two patients who were prescribed two TNF-α inhibitors (adalimumab + infliximab or adalimumab + etanercept) was 44.66±3.05 months.

Table 3. Distribution of patients according to Barkhof criteria, lesion localization on MRI, mean lesion count, and Fazekas scale for asymptomatic white matter lesions

MRI lesion localization	Periventricular	Cortical/juxtacortical	New T2 lesion	Ovoid pattern	Perpendicular to ventricle
Patient group	10	8	N/A	0	0
	Corpus callosum	**Black hole**	**>3 mm lesion**	**Gd-Enhancement**	**Infratentorial/spinal**
	2	2	10	0	0
Barkhof criteria	**0**	**1**	**2**	**>3**	
	6	4	3	2	
Fazekas scaling	**0**	**1**	**2**	**3**	
DWM	2	7	2	0	
PVWM	1	7	3		

SD: Standard deviation, MRI: Magnetic resonance imaging, GD: Gadolinium, DWM: Deep white matter, PVWM: Periventricular white matter

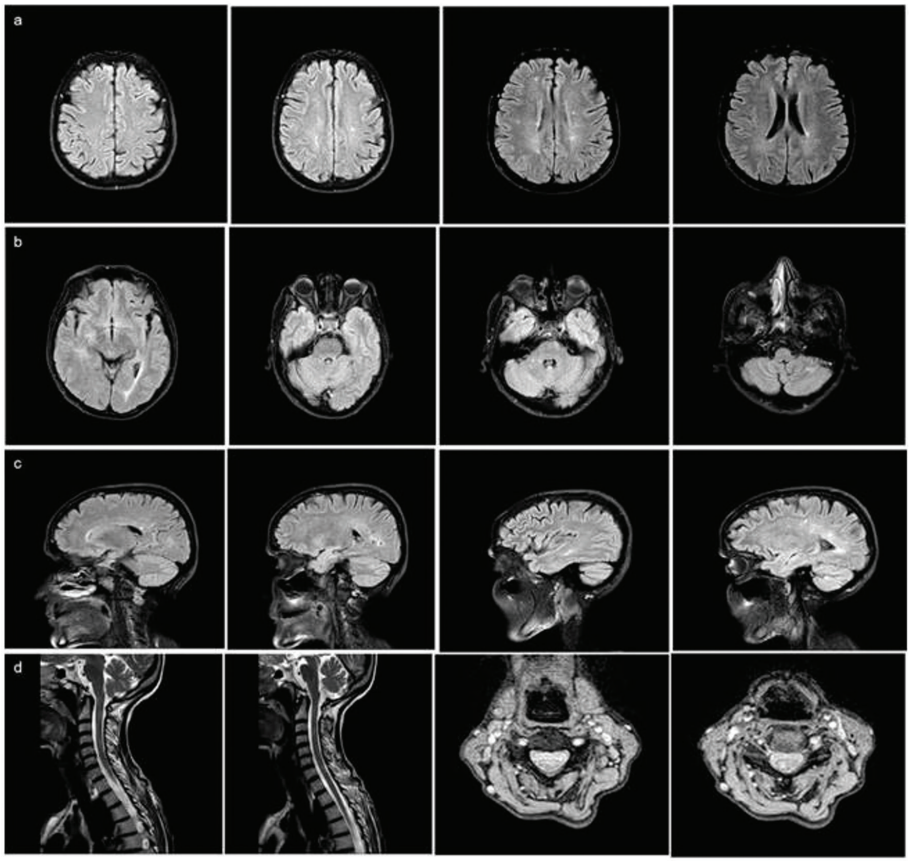

Figure 1. (a, b) Axial and (c) sagittal FLAIR sequences and (d) sagittal-axial T2-weighted magnetic resonance images of the cervical spinal of a patient. Periventricular, cerebellar, pontine and cervical spinal demyelinating lesions are observed

Seven patients had undergone an MRI examination. Of the seven MRIs, three were cervical spine scans, three were brain scans, and one was a brain and cervical spine scan. The MRI lesions in one patient were consistent with that of Neuro-Behçet's disease (involvement of the diencephalon and left temporal lobe). This patient was initially treated with a cyclophosphamide infusion once a month. However, at the one-year follow-up, the lesion had progressed and exhibited contrast enhancement. Thus, treatment with infliximab was initiated, which yielded clinical recovery. After three years of infliximab infusions, he developed ataxia. An MRI was obtained, which showed a hyperintense non-enhancing lesion in the left cerebellar hemisphere. This finding was suggestive of an inflammatory/demyelinating lesion. However, the patient was lost to follow-up.

Representative Case Presentation

A 48-year-old female with idiopathic uveitis presented to the neurology outpatient clinic with facial numbness and an ataxic gait. She had been using adalimumab for three years and was ophthalmologically stable. Neurological examination revealed left facial hypoesthesia and right-sided ataxia. Her MRI revealed periventricular, juxtacortical, right cerebellar, left pontine and cervical spine chronic demyelinating lesions (Figure 1). The thoracic and abdominal CT were reported as normal, and tests for vasculitis were negative. Cerebrospinal fluid (CSF) was obtained via a lumbar puncture. The protein and glucose levels in the CSF were normal, and tests for viruses, microbes, and mycobacterium in the CSF were negative. However, lymphocytes and oligoclonal bands were detected in the CSF. Furthermore, the immunoglobulin G index was 0.4. The MRI findings fulfilled the 2017 McDonald criteria for DIS and DIT. Thus, the patient was diagnosed to have TNF-α inhibitor-associated inflammatory demyelinating disease. The patient was started on subcutaneous methotrexate injections at a dose of 15 mg/week. At the last follow-up, she was clinically and radiologically stable.

Discussion

This study has demonstrated the presence of inflammatory demyelinating diseases of the CNS in patients being treated with TNF-α inhibitors. However, it is still unclear whether the condition is a coincidental finding or caused by the drug (1,9). In our study, almost all the patients had no inflammatory/demyelinating symptom or sign. There are two types of TNF receptors, TNFR1 and TNFR2) (1). TNFR1 mediates apoptosis and demyelination, while TNFR2 activates cell survival, inflammation resolution, and myelination (10).

In a study consisting of 4,391 patients with a 10-year follow-up, the prevalence of neuroinflammation was 0.4% during the treatment with TNF-α inhibitors, making it a rare complication (11). However, after the onset of an inflammatory relapse/lesion, the autoimmune disease process may persist even after the cessation of TNF-α inhibitors. In a four-patient case study, two patients had developed recurrent demyelinating lesions after the treatment had ended. Furthermore, these patients had a family history of autoimmune diseases (1). Despite these findings and the view that latent MS can be aggravated due to TNF-α inhibitor use, no association between drug usage and MS aggravation has been found.

In one study with a long follow-up period, the MRI of most patients showed new lesions or relapses after TNF-α inhibitor cessation, confirming a relapsing CNS demyelinating disease course (12).

A nationwide survey in France identified 33 patients with demyelinating disease of the central and peripheral nervous systems. Of the 22 patients with CNS demyelinating lesions, five were diagnosed as MS according to McDonald's criteria (9). In our study, the asymptomatic MRI lesions were evaluated using the Barkhof criteria, Fazekas scale, and RIS criteria. Most of the lesions were not consistent with an inflammatory demyelinating lesion. In our study, only two patients were symptomatic, and they both had uveitis. One of these patients had findings that met the MS criteria, and the other patient had Neuro-Behçet's disease.

Patients with uveitis who are or are not diagnosed with a rheumatological disease could progress to an inflammatory demyelinating disease course while under treatment with TNF-α inhibitors. Although intermediate uveitis is more frequently present in patients with MS, anterior, posterior and panuveitis can also be seen (12-14). A similar observation was reported by Cunningham and Zierhut (15). They mentioned that there was no apparent evidence that TNF-α inhibitors can directly cause an inflammatory demyelinating disease. However, two of our patients with uveitis developed a demyelinating disease after treatment with TNF-α inhibitors. Furthermore, patients with idiopathic uveitis may exhibit evidence of central demyelination. Therefore, initiation of TNF-α inhibitors in such patients should be undertaken with caution (15).

In our study, only a few patients exhibited symptoms of uveitis. Furthermore, patients with idiopathic uveitis may be at risk for developing inflammatory/demyelinating lesions due to TNF-α inhibitor use because of a possible accompanying or underlying demyelinating disease course.

Study Limitations

The retrospective nature and limited number of participants with demyelinating diseases in the study may not accurately represent the susceptible patient group.

Conclusion

TNF-α inhibitors appear to be safe, and mostly do not aggravate inflammatory or demyelinating lesions. However, using TNF-α inhibitors in patients with idiopathic uveitis may induce an autoimmune CNS reaction/disease.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital (approval number: 514/194/8, date: 27.01.2021).

Informed Consent: Written informed consent was obtained from participants.

Authorship Contributions

Surgical and Medical Practices: A.K.K., R.B., M.E.T., Concept: A.K.K., M.E.T., Design: A.K.K., M.E.T., Data Collection or Processing: A.K.K., R.B., M.E.T., Analysis or Interpretation: A.K.K., R.B., M.E.T., Literature Search: A.K.K., R.B., M.E.T., Writing: A.K.K., R.B., M.E.T.

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