ABSTRACT

The pathophysiologic mechanisms of asthma induced by anti-TNF-alpha treatment are unknown. We report the cases of two patients who developed asthma after starting anti-TNF–alpha treatment of Rheumatoid Arthritis (RA). Cases had no personal or family history of asthma or atopy and had never smoked. No other causes of dyspnea were found.

Key words: Adalimumab, etanercept, asthma

ÖZET


Anahtar kelimeler: Adalimumab, etanercept, astım
Introduction

The pathophysiologic mechanisms of asthma induced by anti-TNF-alpha treatment are not known. Asthma appears to be a definite but rare side-effect of anti-TNF blockade. Asthma symptoms appeared after introduction of anti-TNF-α in two patients who did not appear to be predisposed to the disease (1-5).

Case

We report the cases of two patients who developed asthma after starting anti-TNF-α treatment. Cases had no personal or family history of asthma or atopy and had never smoked. The diagnosis of asthma was made on the basis of recurrent wheezing, breathlessness and coughing in accordance with the definition of the American Thoracic Society. No other causes of dyspnea were found. None of them had blood eosinophilia or rhinosinusitis during anti-TNF-α treatment. Both had never smoked, had not been exposed to any significant air pollution, and had never previously suffered from dyspnea. Total serum IgE levels, assayed before starting asthma treatment, were within the normal range in all patients (3-40 IU/mL). Hypothesis of bronchiolitis was ruled out by high-resolution thoracic CT scan, which was unremarkable. Diffusing capacity of lungs for carbon monoxide was not available. Respiratory treatment involved inhaled steroid and long-acting β2-agonist in cases. The anti-TNF-α treatment was stopped in patient 2 receiving adalimumab because of the emergence of asthma symptoms. The symptoms disappeared within 2 to 3 weeks.

Case-1:
A 49-yr-old lady with a history of seropositive RA was treated with Etanercept for 6 months. Prior to this she had no personal or family history of asthma or atopy and had never smoked. Within 6 months of starting etanercept she developed a diurnal wheeze with shortness of breath, cough and sneezing. Pulmonary Function Tests (PFT) showed a mild obstructive pattern. Asthma treatment was started and symptoms, physical examination and PFT findings were completely recovered within 2 weeks.

Case-2:
A 54-yr-old male with a history of seropositive RA was treated with adalimumab. Prior to this he had no personal or family history of asthma or atopy and had never smoked. Within 3 months of starting adalimumab he developed a diurnal wheeze with shortness of breath. PFT showed a moderate obstructive pattern. Adalimumab was stopped. Asthma treatment was started and symptoms, physical examination and PFT findings were completely recovered.

The chronology of events and absence of previous respiratory disease suggested an adverse reaction to adalimumab and etanercept.

Discussion

Tumor necrosis factor (TNF) alpha has been implicated in asthmatic airway inflammation. The pathophysiologic mechanisms of asthma induced by anti-TNF-alpha treatment are unknown (3,4). Asthma symptoms appeared after introduction of anti-TNF-α in two patients who did not appear to be predisposed to the disease.

Adalimumab is a fully human recombinant monoclonal anti-TNF-α antibody licensed for the treatment of moderate to severely active RA. Like all anti-TNF-α drugs, adalimumab has side-effects, increased susceptibility to infection being the most worrying. Further information revealed that asthma has been reported as an adverse event in 0.3% of adalimumab-treated patients compared with 0.1% of placebo-treated patients (1-3).

The pathophysiologic mechanisms of asthma unmasked by anti-TNF-alpha are unknown, but several hypotheses can be put forward. Our cases make the hypothesis of an allergic reaction to anti-TNF-α unlikely. No skin or anaphylactic symptoms were observed after anti-TNF-α treatment. A possible explanation of the new onset of asthma in these patients lies in the contrasting inflammatory responses in RA compared with asthma and other allergic diseases. Bennett et al (2) suggested an involvement of T helper 1/ T helper 2 balance in the side effects of anti-TNF-α, with a Th1 cytokine decrease, allowing Th2 to be expressed, leading to asthma symptoms. We hypothesize that active RA in this case produced a Th1 cytokine response, which suppressed the clinical expression of asthma. However, once the TNF-α blocking drug was introduced, the Th1 response was suppressed, allowing the Th2-activated pathway to express itself clinically as asthma. TNF-α-blocking drugs might also decrease immunity, playing a role in asthma onset (1,2).

Asthma has been reported as an adverse event to both infliximab and etanercept. There have been reported cases of new onset asthma with etanercept and exacerbations of asthma (1-3,6). In a case report, the most common adverse effects during etanercept treatment were respi-
ratory tract infections (58.8%) and asthma exacerbations (52.9%) (6). Additionally, there have been other cases of reported bronchospasm or wheezing, although most of these have been related to anaphylaxis (1).

The frequency of asthma under anti-TNF-α treatment in patients was reported as 0.74%, as calculated by the number of cases compared with the number of patients treated with anti-TNF-α in a hospital (1). The frequency was reported as 0.3%-1.7% in pivotal trials of anti-TNF-α. However, the frequency may be underestimated because only patients followed up by pulmonologists were reported. Asthma appears to be a definite but rare side-effect of anti-TNF blockade. In most of the adalimumab reported cases the asthma has been mild and adalimumab has not needed to be withdrawn. The details of the asthma adverse events to infliximab and etanercept are not available (1-5). In the absence of other guidelines, we followed the American Thoracic Society (ATS) guidelines for asthma and added an inhaled steroid, which completely resolved the patient’s symptoms but we stopped adalimumab in case (2).

We conclude that asthma in these patients was precipitated by the anti-TNF-α drug adalimumab and etanercept. We recommend careful observation for the RA patients receiving Adalimumab or Etanercept. The use of these drugs is increasing and the adverse effects may become more prevalent in the future. Large randomised controlled trials in which careful account is taken of side effects are needed. To better understand the relationship between anti-TNF-α and the onset of asthma, a prospective follow-up of patients receiving this treatment, including immunologic and virologic tests, must be considered. In cases of severe asthma, anti-TNF-α withdrawal should be considered, whereas anti-TNF-α may be maintained in milder cases of asthma controlled by steroid inhalation. We would recommend careful observation, particularly in patients with a personal or family history of asthma or atopy, and adherence to the ATS guidelines for asthma if symptoms occur.

Kaynaklar