HOW TO TREAT PATIENTS AFTER SERIOUS ADVERSE EFFECTS CAUSED BY TNF INHIBITORS?

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SUMMARY – Biological agents are widely used in the treatment of autoimmune rheumatic disorders. We report on serious adverse events during treatment with anti-tumor necrosis factor antibody in two of our patients with juvenile idiopathic arthritis. One patient was treated with a biological agent due to juvenile idiopathic arthritis complicated by uveitis, developing miliary tuberculosis during treatment. After treatment with antituberculotics, she recovered completely. Her underlying disease is currently in remission. Another patient was treated for juvenile spondyloarthritis and developed an inflammatory process of the central nervous system with serious neurological deficits. He was treated with high-dose corticosteroids, followed by slowly tapering doses of corticosteroids. His neurological deficits improved, but are still present. Similar cases have been described previously, but there are no recommendations how to treat arthritis afterwards in such patients. We would like to emphasize the need of developing guidelines for further treatment of arthritis after the occurrence of serious adverse effects during treatment with biological agents.

Key words: Rheumatology; Arthritis, juvenile; Tumor necrosis factor-alpha – adverse effects; Neurologic manifestation; Tuberculosis, miliary

Introduction

Biological agents have an important role in the treatment of various autoimmune diseases. Their introduction has been a major breakthrough in the treatment of most seriously ill patients who did not respond well to conventional therapy in the field of rheumatology, as well as in some other fields of medicine, having become a cornerstone of their treatment and giving them a new opportunity for a normal life. However, the use of biological agents is associated with a risk of developing adverse effects due to the treatment, some of which may have serious consequences on patient health and can even be potentially fatal1-7. Two cases of serious adverse effects during the treatment of juvenile idiopathic arthritis (JIA) with anti-tumor necrosis factor (TNF) receptor agent adalimumab in our patients have brought to our attention the fact that there are no recommendations and guidelines for further treatment of patient underlying disease after such an adverse event has occurred.

Case Reports

Clinical charts of two patients with serious adverse effects during the treatment with anti-TNF agent were retrospectively reviewed. Reports in the literature describing similar side effects and treatment of patient underlying disease afterwards were analyzed and compared with our experiences.
In our practice, two patients developed serious adverse effects during the treatment of JIA with an anti-TNF receptor agent (adalimumab). The first case was development of miliary tuberculosis in a girl with JIA treated with adalimumab. Our patient was a 7-year-old girl with the polyarticular type of JIA, who had been ill since the age of two. She was treated with a nonsteroidal anti-inflammatory drug (NSAID), methotrexate, and occasionally with intra-articular injections of corticosteroids. By the age of four, she developed bilateral uveitis as a complication of JIA. Initially, she was treated with systemic corticosteroids and methotrexate in combination with topical ophthalmologic therapy (corticosteroids, NSAID and mydriatic eyedrops). Since there was no improvement, therapy with an anti-TNF receptor agent (etanercept) was started. Prior to the introduction of anti-TNF therapy, tuberculin skin test and interferon gamma release assay (IGRA, QuantiFERON test) were performed and they were negative.

The articular component of her disease responded well to biological therapy, but due to the progression of bilateral chronic uveitis, one anti-TNF agent was substituted by another (adalimumab) after one year of treatment. Tuberculin skin test and IGRA were performed and they were negative again, and chest radiography was normal. The switch of therapy was effective and remission of uveitis was induced. Twenty months after the beginning of treatment with adalimumab, she presented with prolonged subfebrile temperatures, loss of appetite, cough and running nose. She was admitted to the hospital, where she became febrile with temperatures over 39 °C and progression of cough, as well as elevated laboratory parameters showing acute inflammation (erythrocyte sedimentation rate (ESR) 43 mm/h, C-reactive protein (CRP) 60.3 mg/L). Thoracic multislice computed tomography (MSCT) scan showed plenty of small nodules diffusely spread over both lungs, in a way specific for miliary tuberculosis (Figs. 1 and 2). Sputum was negative for Mycobacterium (M.) tuberculosis, while the results of IGRA (QuantiFERON test) and M. tuberculosis polymerase chain reaction (PCR) were positive.

Subsequently, we found out that due to deterioration in their social status, her family moved and started living with relatives, one of whom was treated for tuberculosis. She was treated for miliary tuberculosis with combined multidrug antituberculous therapy for 9 months, while treatment with methotrexate and adalimumab was stopped. She is well now, without clinical or laboratory signs of active tuberculosis.

Another patient with serious adverse effects during the treatment with an anti-TNF agent was a boy with
juvenile spondyloarthritis who developed an inflammatory process of the central nervous system (CNS) while he was treated with adalimumab. He had been treated due to JIA since he was four years old. Eventually, he developed sacroiliitis and spondyloarthritis, as well as enthesitis. During the time, he was treated with various NSAIDs, intra-articular and systemic corticosteroids, methotrexate, sulfasalazine and leflunomide. Finally, at the age of 13, because of further progression of the disease, treatment with anti-TNF agent adalimumab was started. Several months later, he was admitted to the hospital because of myositis. Within the next six months he was hospitalized two more times due to chest pain, when he had a rib fracture diagnosed, and due to epididymitis several weeks later. Every time during hospital treatment, anti-TNF therapy was temporarily discontinued, but his rheumatologist at another centre continued treatment afterwards. At the age of 14, 17 months after initiation of anti-TNF treatment, he reported severe headache, vertigo, loss of sense and muscle weakness in his right arm. At that time, he was treated due to juvenile spondyloarthritis with naproxen, sulfasalazine and adalimumab. Adalimumab therapy was promptly and permanently discontinued. He slowly recovered within a week, but not completely, with residual minor muscle weakness and tremor. We suspected the demyelinating process of the CNS, but magnetic resonance imaging (MRI) scans of the brain and cervical spine were normal.

One month later, sudden and severe deterioration occurred with muscle weakness and loss of feeling in his left arm, strong tremor and spontaneous myoclonus of larger groups of muscles of both left arm and leg, progressing in a few days to the right side of the body and exacerbating in intensity. He had accentuated reflexes on the left side of his body up to clonus. Broad spectrum neurological diagnostic workup was done, which showed pleocytosis in cerebrospinal fluid (CSF), with more IgG oligoclonal bands positive, without blood-CSF barrier dysfunction, implicating intrathecal synthesis and an active inflammatory process of the CNS. Treatment with high doses of corticosteroids was initiated, followed by slowly tapering the dose of corticosteroids, while sulfasalazine as a potentially neurotoxic agent was discontinued from therapy. Muscle strength gradually recovered and myoclonia diminished, but still with residual neurological sequel. Repeat MRI scan of the brain and whole spinal cord showed just unidentified bright object (UBO) lesions without signs of demyelination, and repeat CSF analysis within several months showed calming of the inflammatory process of the CNS. All serological tests for potential infectious causes were negative, as well as anti-ganglioside antibodies specific for peripheral neuropathies. No infectious or malignant causes of disease were found. ESR, CRP, complete blood count (CBC), urine and biochemical tests were all normal.

Now he has minor motor asymmetry with mild muscle weakness of the left side of his body, and spondyloarthritis is in a low level of activity. He is currently being treated with naproxen and sulfasalazine that have been reintroduced in treatment.

Discussion

The use of biological agents, including anti-TNF receptor antibodies, is recognized as a risk factor for serious adverse effects, primarily infections. Among the potential causes of infection, one of the most important is *M. tuberculosis*, causing de novo tuberculosis infection or reactivation of latent tuberculosis. There are numerous case reports of tuberculosis infection during anti-TNF therapy in the literature, some of them showing life-threatening conditions. Therefore, it is important to keep this possibility in mind and to screen patients for tuberculosis prior to and during anti-TNF treatment. Guidelines for screening are somewhat different among various authors and include clinical history, physical examination, chest radiography, tuberculin skin test and IGRA.

In our first patient, screening was done prior to the introduction of anti-TNF treatment and then again before the switch of therapy, and it was negative on both occasions. The problem occurred during treatment when she and her family, due to deterioration in their social status, moved to live with their relatives, one of whom was treated for tuberculosis: Additional obstacle in our way was the fact that they kept it secret. Fortunately, the diagnosis was established in time to prevent serious complications, and she is now cured of tuberculosis.

Among various adverse effects of anti-TNF treatment, neurological adverse events are amongst those that occur more often. The most often events are CNS
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demyelination, optic neuritis, peripheral neuropathy and facial palsy, whereas transverse myelitis, progressive multifocal leukoencephalopathy, cerebrovascular disease, encephalopathy and CNS infections are not as often as those mentioned previously.²,³,⁴,¹⁴,¹⁵.

In our patient, we immediately suspected a demyelinating process but repeat MRI scans of the CNS did not show demyelinating lesions. We found signs of active inflammatory process of the CNS, most likely of autoimmune origin, since all of the possible infectious causes were excluded. Our patient responded well to corticosteroid therapy, but there are still residual minor neurological deficits present.

There are numerous other possible adverse effects of biological therapy that a clinician should be aware of, such as infusion reactions, immune system disorders, hematologic adverse events, lung disease, cardiovascular effects of biologicals, sarcoidosis, as well as the possible relationship between biological agents and malignant disease.¹

However, once such an adverse event occurs and after it is taken care for, there still remains a fact that we have a patient with rheumatic disease that was severe enough to require biological therapy due to the lack of disease control with conventional treatment, leaving us in a difficult situation of having to decide on further therapy of the underlying disease. Individual experiences reported in the literature are scarce, and to the best of our knowledge, there are no recommendations or guidelines for further treatment of such patients.⁵

Considering our patients, in the girl with JIA and chronic uveitis, who was treated for miliary tuberculosis, in case of another flare of disease, we are planning to start treatment with the interleukin-6 inhibitor tocilizumab, whereas in the boy with juvenile spondyloarthritis and inflammatory process of the CNS, we do not intend to reintroduce biological therapy for the following two reasons: first, the etiology of inflammatory process is not completely resolved, even though we believe that it is an autoimmune process initiated by anti-TNF therapy, and second, neither the boy or his family are willing to start biological treatment again.

During the treatment with biological agents, adverse events may occur, but there are no recommendations how to treat patients afterwards. We would like to emphasize the need of creating and developing guidelines for further treatment of such patients at the level of international expert societies, and on the principles of evidence-based medicine as far as it is possible.

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Sažetak

KAKO LIJEČITI BOLESNIKE NAKON TEŠKIH NEŽELJENIH DJELOVANJA UZROKOVANIH INHIBITORIMA TNF

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Biološki lijekovi se primjenjuju u liječenju brojnih autoimunih reumatskih bolesti. U ovom članku prikazujemo dva slučaja ozbiljnih nuspojava liječenja inhibitorima čimbenika nekroze tumora (tumor necrosis factor, TNF) kod bolesnika s juvenilnim idiopatskim artritisom (JIA): bolesnice liječene zbog JIA kompliciranog razvojem uveitisa, kod koje se javila milijarna tuberkuloza tijekom liječenja. Nakon liječenja antituberkuloticima došlo je do potpunog oporavka. Njena osnovna bolest je u remisiji. Drugi bolesnik je liječen zbog juvenilnog spondiloartritisra te je razvio upalni proces središnjega živčanog sustava s ozbiljnim neurološkim posljedicama. Liječen je visokim dozama kortikosteroida koje su potom postupno snižavane. Neurološki ispadi su se dijelom poboljšali, ali su ipak još uvijek prisutni. Slični slučajevi su opisivani i ranije, ali nema preporuka kako bi trebalo liječiti artritis nakon što nastupe takve nuspojave. Željeli bismo naglasiti potrebu stvaranja smjernica za daljnje liječenje artritisra nakon pojave teških nuspojava prilikom liječenja biološkim lijekom.

Ključne riječi: Reumatologija; Artritis, juvenilni; Faktor tumorske nekroze-alfa – štetno djelovanje; Neurološke manifestacije; Tuberkuloza, milijarna