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SHORT COMMUNICATION

Drug-induced lupus in anti-TNF-alpha therapy and its treatment with rituximab

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Abstract We report three patients with rheumatoid arthritis (RA) who were treated with anti-TNF-α agents and who developed drug-induced lupus (DIL). Two of them received etanercept and the remainder adalimumab. We also present the favorable response observed with the withdrawal of the anti-TNF-alpha agents and the introduction of rituximab. Through this intervention, we observed a very good control of the activity of both DIL and RA without additional adverse reactions.

Keywords Rheumatoid arthritis · Etanercept · Adalimumab · Drug-induced lupus · Rituximab

Introduction

Several anti-TNF-alpha agents have been approved for the treatment of RA, psoriasis, psoriatic arthritis and Crohn's disease [1]. Nowadays, they are widely used around the world. The most commonly reported adverse reactions to their administration have been infections, malignancies, demyelinating diseases, development of autoantibodies and DIL [2]. There are no current recommendations for the treatment of this latter complication other than the withdrawal of the medication, increase o to start steroids and/or immunosuppressors. We report three patients who developed DIL by anti-TNF-alpha agents who favorably responded to the withdrawal of these drugs and to start rituximab therapy.

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Case report

In the Valle del Lili Foundation, a referral hospital in southwestern Colombia, 955 patients with the diagnosis of RA were treated between June 2001 and December 2010. Among them, 60 required the prescription of any of the 3 available anti-TNF-alpha agents: 38 received etanercept, 12 adalimumab and 10 infliximab. Only three of those patients developed a DIL, and these cases are the subject of this report.

Case 1

42-year-old woman who has been diagnosed with RA 6 years before. Her disease was characterized by severe erosive polyarthritis, presence of early rheumatoid nodules in elbows and high titers of rheumatoid factor. No other autoantibodies were present by the time of the diagnosis. She also presented with dry eyes confirmed by a Schirmer's test. The patient had been treated with sulfasalazine (interrupted because of the development of polymorphic erythema) and also with prednisolone, methotrexate and leflunomide at standard doses without favorable response. Etanercept was prescribed after obtaining a negative tuberculin test and a normal X-ray. She had an early favorable response with this medication, but 7 months after the initiation of it, presented with fever, malaise, polyarthralgias, alopecia and urticarial vasculitis confirmed by biopsy. The following tests were obtained: positive antinuclear antibodies (1:5120), positive anti-DNA (1:640), lymphopenia (absolute lymphocyte count of 1,160/mm^3)

Table 1 Characteristics of RA, the anti-TNF-alpha utilized, the time of lupus onset after at anti-TNF-alpha treatment and the manifestations of DIL

Case	Age of RA diagnosis (Years)	Characteristics of RA	Anti-TNF-alpha	Time of lupus onset at anti-TNF-alpha treatment	Manifestation related to DIL
1	36	Erosive seropositive with nodules	Etanercept	7 months	Lymphopenia, alopecia,urticarial vasculitis
2	32	Erosive seropositive	Etanercept	3 years	Lymphopenia, proteinuria, anemia
3	28	Erosive seropositive with nodules	Adalimumab	1 year	Raynaud's phenomenon, vasculitis, fever, leukopenia

RA rheumatoid arthritis, *DIL* drug-induced lupus

and positive anti-Ro antibodies. The sum of these clinical findings and the laboratory results leaded to the diagnosis of DIL by anti-TNF-alpha. The patient as admitted, the etanercept was withdrawn, transiently we increased of steroid and rituximab was introduced at doses of 1 g initial and 1 g 2 weeks after. The patient improved and she presented remission of the symptoms of vasculitis, alopecia, leukopenia and remains without arthritis symptoms. Steroid requirements could be lowered.

Case 2

52-year-old woman who presented with polyarthralgias (hands, shoulders, cervical spine, left knee, ankles, feet). Her blood count reported 8,500 leukocytes, 6,035 neutrophils, 1,700 lymphocytes, 136,000 platelets and a hemoglobin level of 9.5 mg/dl. She had a positive history of seropositive RA that was diagnosed at the age of 32. She did not present with other autoantibodies positivity at the moment of the diagnosis. The disease remained active spite of the regular treatment with prednisolone and various disease modifying antirheumatic drugs so etanercept was prescribed 3 years before. The immunologic studies obtained reported positive antinuclear antibodies (1:640 homogenous pattern), positive anti-DNA (1:20), positive anti-Ro antibodies and 768 mg of proteins in a 24-hour urine sample. Pulses of methylprednisolone was begun and rituximab at doses of 1 g initial and 1 g 2 weeks after. The patient experimented regression of the symptoms and 5 months later the proteinuria disappeared. There has not been clinical activity of the arthritis since then. The oral steroid dose could be tapered to 5 mg of prednisolone daily.

Case 3

36-year-old woman was diagnosed with seropositive rheumatoid arthritis 8 years before. She had rheumatoid nodules, erosive lesions in hands and xeroftalmia. By the time of the diagnosis, she had antinuclear antibodies with a speckled pattern (1:80). Her disease did not respond properly to the conventional treatments as steroids, methotrexate, hydroxychloroquine, sulfazalacin and leflunomide so it was decided to begin the use of adalimumab with a good clinical response. The steroids could be withdrawn. A year later, she presented with worsening dry symptoms, vasculitis lesions on the lower limbs, severe joint pains, Raynaud in hands, weight loss, anorexia, fever (37.8°C). A series of laboratory tests were done: antinuclear antibodies were reported in 1:320, anti-Ro antibodies positive, leukopenia and decreased levels of complement (C3 and C4). The adalimumab was withdrawn, 50 mg of prednisolone and rituximab 1 g was introduced and it was repeated 2 weeks later at the same dose. She recovered from the symptoms described. One year after, she was asymptomatic with normal laboratories analysis. The steroid was withdrawn.

Table 1 resumes the main characteristics of three patients.

Comment

The generation of autoantibodies induced by anti-TNF-alpha agents has been estimated to occur between 14 and 70% among individuals after a 1-year follow-up period [3]. Despite this high frequency, the clinical lupus syndrome is not common. This may reflect the existence of predisposing genetic and/or environmental factors [4]. There are certain proposed mechanisms for development of DIL related to anti-TNF-alpha therapy. The inhibition of TNF-alpha may induce the apoptosis of cells that express this molecule with release of nucleosomes and begin autoreactivity to them [3]. It has also been proposed that TNF-alpha may regulate the expression of CD44, a molecule involved in the clearance of apoptotic neutrophils by the phagocytes, phenomena that have been described earlier in patients with lupus [5]. Other implicated mechanism is the increase of B cell-activating factor of the tumor-necrosis factor family (BAFF) expression observed in patients treated with anti-TNF-alpha agents. The BAFF is a potent activator of B cells and is up-regulated in many autoimmune diseases in

human such as systemic lupus erythematosus, RA and Sjögren's syndrome [6, 7].

There are not current recommendations for the treatment of DIL in anti-TNF-alpha therapy. Because the most probable mechanism is the B cell activation, we proposed that its depletion is a rational therapeutic strategy.

The use of rituximab in RA patients with DIL related to anti-TNF-alpha was efficacious and safe in three cases.

Conflict of interest None.

References

1. Nash PT, Florin TH (2005) Tumour necrosis factor inhibitors. Med J Aust 183:205–208
2. Hochberg MC, Lebwohl MG, Plevy SE et al (2005) The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. Semin Arthritis Rheum 34:819–836
3. Williams EL, Gadola S, Edwards CJ (2009) Anti-TNF-induced lupus. Rheumatology (Oxford) 48:716–720
4. De Bandt M (2006) Lessons for lupus from tumor necrosis factor blockade. Lupus 15:762–767
5. Cairns AP, Crockard AD, McConnell JR et al (2001) Reduced expression of CD44 on monocytes and neutrophils in systemic lupus ertihematosus: relations with apoptotic neutrophils and disease activity. Ann Rheum Dis 60:950–955
6. Groom JR, Fletcher CA, Walters SN et al (2007) BAFF and MyD88 signals promote a lupus like disease independent of T cells. J Exp Med 204:1959–1971
7. Pers JO, Daridon C, Devauchelle V et al (2005) BAFF overexpression is associated with autoantibody production in autoimmune diseases. Ann N Y Acad Sci 1050:34–39