

Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients

Kilian Verschueren · Els Van Essche ·
Patrick Verschueren · Veerle Taelman ·
Rene Westhovens

Received: 8 February 2007 / Accepted: 11 February 2007 / Published online: 6 March 2007
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Abstract We report two rheumatoid arthritis patients developing sarcoidosis possibly induced by etanercept. Both women, aged 46 and 53, had erosive, rheumatoid-factor-positive rheumatoid arthritis (RA) for 7 and 6 years, respectively. The eldest had received infliximab for over a year with good response, which was stopped because of a perfusion reaction. She developed a cough and dyspnea after 6 months of etanercept treatment. The other developed erythema nodosum and a plaque lesion on the right arm after 1 year of etanercept. Imaging showed, in both cases, mediastinal adenopathies. Biopsies were compatible with sarcoidosis. Etanercept withdrawal led to a complete remission. Recently, there have been reports of noninfectious granulomatous syndromes in patients receiving etanercept for a variety of diseases. In our cases, the temporal association with etanercept therapy and the complete remission after suspension of etanercept suggest a triggering role of this agent. Possible mechanisms of action and supporting evidence are discussed.

Keywords Etanercept · Granuloma · Infliximab · Rheumatoid arthritis · Sarcoidosis

K. Verschueren · P. Verschueren · V. Taelman · R. Westhovens
Department of Rheumatology, University Hospitals Leuven,
Katholieke Universiteit Leuven,
Leuven, Belgium

E. Van Essche
Rheumatology Mol,
Rondplein 8, 2400 Mol, Belgium

R. Westhovens (✉)
Universitair Ziekenhuis Leuven,
Herestraat 49, 3000 Leuven, Belgium
e-mail: rene.westhovens@uz.kuleuven.ac.be

Introduction

Tumor necrosis factor-alpha (TNF- α) blockade with the monoclonal antibody infliximab, as well as with the soluble receptor fusion protein etanercept, is effective in the treatment of inflammatory diseases such as rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, and psoriasis vulgaris, although differences in efficacy and side effects have been reported [1]. In addition, infliximab is effective in chronic granulomatous diseases such as Crohn's disease (CD), sarcoidosis, and Wegener granulomatosis, while etanercept is not [2]. However, treatment with infliximab bears an increased risk of granulomatous infections compared to etanercept [2, 3].

Recently, there have been reports of several syndromes characterized by noninfectious granuloma formation in patients receiving etanercept for a variety of diseases [4].

We report two RA patients developing sarcoidosis possibly induced by etanercept and discuss mechanisms of action.

Case report

Patient 1 is a 53-year-old white woman with a 6-year history of erosive, rheumatoid-factor- (RF) positive RA. Her disease has been poorly responsive to intramuscular gold, methotrexate, and leflunomide. The treatment with infliximab in combination with methotrexate from August 2002 until November 2003 showed a good response but was stopped because of a perfusion reaction. Methotrexate was continued at a dose of 15 mg/week. In June 2004, due to persistent disease activity with increased erythrocyte sedimentation rate (ESR) of 69 mm/h and C-reactive protein level (CRP) of 107.8 mg/l (normal value ≤ 5.0),

treatment with etanercept (25 mg twice weekly) was started. Methotrexate was continued at a dose of 10 mg/week. Two months later, there was clinical improvement and acute-phase reactant levels were virtually normal. A purified protein derivative (PPD) skin test and a chest radiograph performed before etanercept therapy were normal.

After 6 months, the patient developed a cough and dyspnea, accompanied by a weight loss of 7 kg over a period of 2 months. An X-ray and a computed tomography of the chest revealed a reticulonodular pulmonary infiltrate and bilateral hilar and paratracheal adenopathies that showed as hyper metabolic lesions on [18F]fluorodeoxyglucose positron emission tomography. A bronchoscopy with transbronchial needle aspiration and mediastinoscopy with biopsy of mediastinal adenopathies were performed. The histology showed noncaseating granulomas of the sarcoid type. Malignancy was excluded. The tissue stains and cultures for bacteria, mycobacteria, and fungi and a new PPD skin test remained negative. The angiotensin-converting enzyme (ACE) level was mildly elevated at 75 U/l (reference range, 18–55 U/l); the ESR was 10 mm/h and the CRP 16.9 mg/l. These findings were consistent with the diagnosis of sarcoidosis.

Empiric tuberculostatic treatment was given until definite negative results of mycobacterial cultures. The methotrexate therapy was withdrawn for only a few weeks.

Etanercept therapy was stopped. The treatment with oral methylprednisolone at an initial dose of 32 mg daily, which was slowly tapered to 4 mg daily, led to complete clinical and radiological remission within the following 12 months. The ACE levels reverted to normal.

Patient 2 is a 46-year-old white woman with a 7-year history of erosive, RF-positive RA. She had an incomplete clinical response and intolerance to several disease-modifying drugs including methotrexate. In October 2003, due to persistent clinical activity, etanercept (25 mg twice weekly) was started, with good response. The patient had received tuberculostatic treatment for 9 months in 1977 after exposure to *Mycobacterium tuberculosis*. However, given the negative PPD skin test and the normal chest radiograph before etanercept therapy, no prophylactic tuberculostatic treatment was given.

One year later, the patient developed erythema nodosum of the legs and a plaque lesion on the right forearm. A skin biopsy showed septal panniculitis. An X-ray and a computed tomography of the chest revealed bilateral hilar and paratracheal adenopathies. A bronchoscopy with transbronchial needle aspiration and mediastinoscopy with biopsy of mediastinal adenopathies were performed. The histology showed noncaseating granulomas of the sarcoid type. Malignancy was excluded. The tissue stains and cultures for bacteria, mycobacteria, and fungi remained

negative. The ESR and CRP were in normal range. These findings were consistent with the diagnosis of sarcoidosis.

Etanercept was stopped. No additional therapy was given. In the following months, complete clinical and radiological remission was observed.

Discussion

Sarcoidosis is a systemic granulomatous disease of unknown origin that primarily affects the lung and lymphatic systems, although it can involve all organ systems. The diagnosis is established on clinicoradiological findings supported by histological evidence of noncaseating epithelioid cell granulomas. Other diseases with similar presentation have to be excluded, especially mycobacterial infections. There is evidence that inflammation and granuloma formation occurs in a genetically susceptible host as a result of a Th1-type immune response triggered by an antigen and is characterized by large numbers of activated macrophages and CD4+ T lymphocytes [5]. Of the great variety of cytokines produced, interferon- γ , TNF- α , interleukin (IL)-12, and IL-18 play a critical role in driving the Th1 commitment in the course of the granulomatous process [6].

As there is wide evidence of the pivotal role of TNF- α in the induction and maintenance of inflammation and granuloma formation, TNF- α -blocking therapy has been used in the treatment of refractory sarcoidosis. Significant improvement was reported with infliximab in more than 30 cases [7, 8]. In contrast, 11 of 16 patients with progressive pulmonary sarcoidosis treated with etanercept had worsening of the disease [9].

We report the development of sarcoidosis in two patients with RF-positive RA after 6 months and 1 year of etanercept therapy, respectively. Although a rare association between sarcoidosis and RA has been described [10], the temporal association with etanercept therapy and the improvement of the clinical, radiological, and biochemical manifestations of the disease after the suspension of etanercept suggest a possible triggering role of this agent. It is important to note that our first patient was treated with infliximab before, without similar complications. Moreover, several syndromes of noninfectious granuloma formation in patients receiving TNF- α -blocking therapy have been reported, and all but one had received etanercept [4].

Despite the common therapeutic target, infliximab and etanercept have different kinetics and mechanisms of action, resulting in differences in efficacy and side effects [2, 3]. Current evidence suggests that infliximab, but not etanercept, disrupts established granulomas [2]. This may not only account for the lower risk of reactivation of tuberculosis with etanercept compared to infliximab, but

also may be the reason why etanercept is not effective in chronic granulomatous diseases such as sarcoidosis. The following underlying mechanisms support this hypothesis.

Differences in administration and clearance between etanercept and infliximab result in higher peak concentrations and higher steady-state drug levels of the latter, possibly causing greater and more prolonged TNF- α suppression [3]. Because of differential binding avidities for soluble versus transmembrane TNF- α , infliximab inhibits both TNF receptor p55- and p75- (TNFRp75) mediated events, whereas etanercept leaves TNFRp75 signaling partially intact. Furthermore, infliximab binds TNF- α fast and irreversibly in vitro. Etanercept, however, has both high-on and high-off-binding kinetics, which might favor the redistribution of TNF- α from sites of production to sites where the concentration is low without completely blocking the bioactivity at the production sites [2].

Infliximab causes in vitro antibody- and complement-dependent lysis of cells expressing membrane-associated TNF- α , while no such reports exist with etanercept. Infliximab also caused apoptosis in monocytes and lamina propria T cells from patients with CD, while etanercept has been shown to cause apoptosis in monocytes and macrophages, but not in lymphocytes, of RA patients [3].

Of the other cytokines involved in the granulomatous process, infliximab has been shown to inhibit interferon- γ production, while etanercept does not [3]. Moreover, in ankylosing spondylitis patients, infliximab therapy caused a highly significant reduction in the numbers of CD4+ T cells and CD8+ T cells expressing interferon- γ or TNF- α , whereas etanercept therapy caused a highly significant increase in the numbers of the same cells [11]. Based on these findings, one could speculate about a possible facilitating or even triggering role of etanercept in the development of sarcoidosis in our patients.

In summary, we report two RA patients developing sarcoidosis during etanercept therapy. Our findings, along with other cases of noninfectious granulomatous syndromes

in patients receiving TNF- α blockade with etanercept but not with infliximab, together with the poor results of etanercept in chronic granulomatous diseases, show that important granuloma formation remains possible under etanercept and suggest a triggering role of this agent in the reported syndromes.

Acknowledgement R. Westhovens is a consultant for Schering–Plough and BMS.

References

1. Haraoui B (2005) Differentiating the efficacy of the tumor necrosis factor inhibitors. *Semin Arthritis Rheum* 34(Suppl 1):7–11
2. Wallis RS, Ehlers S (2005) Tumor necrosis factor and granuloma biology: explaining the differential infection risk of etanercept and infliximab. *Semin Arthritis Rheum* 34(5 Suppl1):34–38
3. Furst DE, Wallis R, Broder M et al (2006) Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. *Semin Arthritis Rheum* 36(3):159–167
4. Gonzalez-Lopez MA, Blanco R, Gonzalez-Vela MC et al (2006) Development of sarcoidosis during etanercept therapy. *Arthritis Rheum* 55(5):817–820
5. Nunes H, Soler P, Valeyre D (2005) Pulmonary sarcoidosis. *Allergy* 60(5):565–582
6. Ziegenhagen MW, Muller-Quernheim J (2003) The cytokine network in sarcoidosis and its clinical relevance. *J Intern Med* 253:18–30
7. Keystone EC (2004) The utility of tumour necrosis factor blockade in orphan diseases. *Ann Rheum Dis* 63(Suppl 2):ii79–ii83
8. Doty JD, Mazur JE, Judson MA (2005) Treatment of sarcoidosis with infliximab. *Chest* 127:1064–1071
9. Utz JP, Limper AH, Kalra S et al (2003) Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. *Chest* 124:177–185
10. Kucera RF (1989) A possible association of rheumatoid arthritis and sarcoidosis. *Chest* 95(3):604–606
11. Dinarello CA (2005) Differences between anti-tumor necrosis factor- α monoclonal antibodies and soluble TNF receptors in host defense impairment. *J Rheumatol Suppl* 74:40–47