Case Report

Treatment of severe refractory erythema nodosum leprosum with tumor necrosis factor inhibitor Etanercept

Sundeep Chowdhry, Akhilesh Shukla*, Paschal D’souza, Tapan Dhali, Prashansa Jaiswal

Department of Dermatology, Venereology, and Leprology, ESI-Postgraduate Institute of Medical Sciences and Research, New Delhi, India

ARTICLE INFO

Article history:
Received 9 December 2015
Received in revised form 29 January 2016
Accepted 4 February 2016
Available online 24 February 2016

Keywords:
Biologics
Etanercept
Erythema nodosum leprosum
Leprosy
Treatment

ABSTRACT

Erythema nodosum leprosum (ENL) is a common complication of lepromatous leprosy. Some patients unresponsive to conventional, first-line therapeutics develop recurrent, recalcitrant ENL. Here, we report a case of severe refractory ENL that was successfully treated with Etanercept. Biologics may be considered as therapeutic alternatives in management of severe, recalcitrant ENL.

© 2016 Asian-African Society for Mycobacteriology. Production and hosting by Elsevier Ltd. All rights reserved.

Case Report

Leprosy (LR) is a chronic infectious disease caused by Mycobacterium leprae. It is primarily a disease of the peripheral nervous system and skin, but other organs may also be involved. Erythema nodosum leprosum (ENL), the most common manifestation of type 2 LR (T2LR), is an immune complex–mediated complication of lepromatous leprosy (LL). T2LR presents with skin lesions (red, painful, and tender subcutaneous lesions), fever, and systemic inflammation that may affect the nerves, eyes, joints, testes, and lymph nodes [1]. Although mild episodes of ENL can be treated symptomatically with anti-inflammatory agents [non-steroidal anti-inflammatory drugs (NSAIDS)] and usually resolve spontaneously, more severe cases (i.e., those with nerve involvement or systemic involvement) require systemic therapy, such as steroids and Thalidomide, to manage the reactionary state of the disease and prevent permanent residual complications.

Here, we present a patient with severe ENL who was successfully treated with Etanercept, a tumor necrosis factor alpha (TNF-α) inhibitor; as he was refractory to treatment with conventional therapies.

A 49-year-old man diagnosed as a case of nodular LL (in his 2nd month of multidrug anti-leprosy treatment) and diabetes...
mellitus presented to the Department of Dermatology with a 1-week history of erythematous, tender papules, and nodules over his forearms, trunk, thighs, buttock, and calves, accompanied by high-grade fever, myalgia, and inguinal lymphadenopathy. He also had severe neuritis of the ulnar and radial cutaneous nerve. Laboratory investigations showed increases in total leukocyte count (16,000/mm³), anemia (hemoglobin: 9 g/dl), raised erythrocyte sedimentation rate (36 mm/h), random blood sugar (178 mg/dL), elevated TNF-α (19 pg/mL) and interleukin 6 (IL6; 4 pg/mL). Slit skin smears from all three sites (eyebrows, ear lobes, and skin nodules) showed solid stained acid-fast bacilli, with few fragmented and granular acid-fast bacilli, arranged in globi (Fig. 1). Therefore, our final grading of the bacteriological index was 6+, and the skin biopsy from one of the nodules was consistent with ENL.

After making a diagnosis of severe ENL, the patient received oral Prednisolone (40 mg) in addition to his anti-leprosy multidrug therapy (MDT), comprised of 600 mg of monthly Rifampicin, 300 mg monthly of Clofazimine, 100 mg Dapsone, and 50 mg Clofazimine daily. Supportive treatment in the form of NSAIDS and multivitamins was also instituted. However, after initial improvement following Prednisolone treatment for 2 weeks, the patient again developed new tender erythematous lesions of ENL associated with malaise and fever. Over the next 6 months, despite multiple extended courses of Prednisolone in higher doses (40–80 mg daily), Clofazimine (300 mg daily), Thalidomide (starting dose: 300 mg daily), Minocycline (100 mg daily), Clarithromycin (1 g daily), Ofloxacin (400 mg daily), Pentoxifylline (400 mg three times daily), and Azathioprine (150 mg daily; later increased to 300 mg), the patient had few symptom-free periods and experienced many ENL-related episodes with increased severity of lesions in the form of numerous necrotic lesions (Fig. 2, neuritis, and severe systemic manifestations, including epididymo-orchitis and lymphadenitis.

The patient developed adverse effects, such as oral candidiasis, abdominal pain, and diarrhea due to above-mentioned medications. There was aggravation of peripheral neuropathy after starting Thalidomide, which was then discontinued. He also developed uncontrolled diabetes mellitus and hypertriglyceridemia (670 mg/dL) due to prolonged steroid therapy. These complications were not only difficult to manage, but they were aggravated with medication for ENL.

Given the severity of patient symptoms despite the use of standard therapies, alternative management strategies were considered, and we decided to start the patient on Etanercept. Before starting Etanercept, the patient underwent a series of investigations to rule out any underlying immunosuppression or latent foci of tuberculosis in the form of a Mantoux test, chest X-ray, interferon-gamma release assay, and Hepatitis B and HIV serologies. Since there was no abnormality detected in any of the above-mentioned investigations, Etanercept was administered in a dose of 50 mg/week subcutaneously. The patient showed signs of improvement within 48 h of the first dose in the form of decreases in constitutional

Fig. 1 – Globi arrangement of acid-fast lepra bacilli.

Fig. 2 – Multiple deep punched-out necrotic ulcers of erythema nodosum leprosum.
symptoms and evidence of healing of deep necrotic ENL lesions. After receiving Etanercept for 12 weeks, the patient improved significantly (Fig. 3), allowing for a slow taper and eventual discontinuation of Prednisolone.

The patient was continued on 50 mg/week Etanercept (thirteenth dose of injection) and MDT and consequently did not have a recurrence of ENL. After 16 weekly injections of Etanercept, we proposed tapering the dose to biweekly and gradually discontinued the same over a period of time.

The underlying immunopathological mechanism for ENL remains unclear. ENL has traditionally been considered an immune complex–mediated phenomenon with an accompanying vasculitis [2–4]. However, high levels of TNF-α and IL6 are consistently found in patients with more severe forms of the disease, suggesting that a cell-mediated immune response also plays a role [5]. This provided the rationale for the use of TNF-inhibitory agents reported by Faber et al. (who used Infliximab) [6] and Ramien et al. (who used Etanercept) [7] when conventional therapies were not sufficient to control symptoms.

Since Etanercept is less costly, has better patient convenience (comes in self-administered injections), and causes less immunosuppression relative to Infliximab, we chose to treat our patient with Etanercept.

The impressive clinical response of our patient to Etanercept, along with similar reports by Faber et al. [6] and Ramien et al. [7] to Infliximab and Etanercept, respectively, provided additional evidence to support an important role of TNF-α in the pathogenesis of severe ENL, as well as established them as promising treatments for these patients. However, utmost care should be taken to look for reactivation of tuberculosis and immunosuppression. Further research to determine the role of TNF-α in the pathogenesis of ENL is needed. In conjunction, randomized controlled trials are necessary to establish the role of inhibition of TNF-α in treating patients who have severe recalcitrant ENL that is unresponsive to standard conventional therapy.

Conflict of interest

No conflict of interest to declare.

REFERENCES