Etanercept and urticaria in patients with juvenile idiopathic arthritis

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ABSTRACT

Etanercept, a tumor necrosis factor receptor p75 Fc fusion protein (TNFR:Fc; Enbrel®), has preliminarily been shown to be effective in the management of methotrexate-resistant polyarticular juvenile idiopathic arthritis (JIA). Reported side-effects have been minor, for example injection site reactions and upper respiratory tract infections, not necessitating discontinuation of the medication (1, 2). We report on 2 patients who developed an urticaria-like rash with prurigo appearing bilaterally on the extensor surfaces of the elbows subsequent to etanercept injections.

Case reports

Case 1

This girl was 2 years old when her joint symptoms became apparent in 1991, and JIA was diagnosed (oligoarthritis, later extended oligoarthritis, RF-, ANA-, HLA-B27+). In view of the high disease activity despite auranofin (years used 1991-92/ 5 months of use before etanercept), aurothiomalate (1992-94/ 23 mo.), hydroxychloroquine (1992/ 1 mo.), methotrexate (1993-99/ 74 mo.), cyclosporine (1997-99/ 26 mo.), and sulphasalazine (1992/ 4, 1997/ 2 mo.), numerous intra-articular glucocorticoid injections were given during the years in question. In the winter of 1998-99 she also had several infectious conditions and was given 5 intravenous (IV) immunoglobulin infusions.

Subcutaneous etanercept treatment (Enbrel® 0.4 mg/kg) twice a week was introduced on May 17, 1999, added to the regimen of cyclosporine (2.2 mg/kg/d), methotrexate (subcutaneous injection, 7mg/m2/week), glucocorticoid (Calcort® 0.4 mg/kg on alternate days) and naproxen (7.5mg/kg/d). Subsequently, the glucocorticoid dose could be reduced by 50% and no local steroid injections were needed for 5 months.

On September 3, 1999 etanercept and methotrexate were discontinued on account of acute eczema with a secondary bacterial infection, and antibiotic treatment was started. An etanercept injection was given on September 13, but since prurigo appeared on the morning of September 16, the drug was again withheld. Joint symptoms had returned by the time the infection was eliminated in October. Methotrexate and etanercept were re-introduced on October 6 and 11, respectively. Again, etanercept therapy had to be interrupted after an injection on October 18, because a few days later a new red, palpable, papula/urticaria-like rash with prurigo appeared bilaterally over an area the size of her palm on the extensor side of the elbow skin. The rash was similar to that seen prior to the secondary infection. The rash was fixed, and after subsequent injections appeared on the extensor surfaces of the knees as well, together with a 5 x 3 cm area under the left axilla. The pruritus was not generalized but felt only on the site of the skin manifestations. The upper eyelids swelled with a reddish rash without papules. No eosinophilia was detected in the blood count during treatment with etanercept.

The patient had never had urticaria or eosinophilia, but suffered from dry skin with occasional eczema, mainly on the back of her hands.

As her arthritis flared up again, IV immunoglobulins (1 g/kg/4 weeks) were reintroduced on November 10. The following day the urticarial papules, which had persisted for a fortnight, had totally blanched, only the effects of scratching remaining, and she had no itching. Encouraged by this, etanercept injections were reintroduced and infusions have been continued once a month. This has cleared the skin eruption, only a few solitary papules appearing on the back of the elbows a few days before the next infusion is due. In addition to the gammaglobulin infusions she is being kept on methotrexate, naproxen and a trace of glucocorticoids. She is also free from arthritic symptoms.

Case 2

The second girl was 4 years old when she started to limp in 1996. JIA (polyarthritis, RF-, ANA-, HLA-B27+) was diagnosed in the spring 1997, and she came under our care after the disease had proved resistant to treatment with aurothiomalate (1997-98/ 14 mo.), hydroxychloroquine (1997/ 7 mo.), methotrexate

(1997-99/ 26 mo.) and glucocorticoids (1997-99/ 30 mo.). IV immunoglobulin therapy (1999/ 2 mo.) had to be discontinued because of severe headaches. Oral cyclosporine (1998-99/ 12 mo.) was added to her medication, but no remission was achieved. Treatment with injectable gold had been discontinued after 2 months in April 1998 due to a reddish, itching rash, which was taken to be of allergic origin, since she complained simultaneously of pruritus in her eyes and ears. Sulphasalazine was discontinued in August 1998 after two months' therapy because of a slight reddish rash on her knees, left elbow and wrist; the rash did not itch. She also had a positive red dermographismus sign.

Subcutaneous etanercept therapy (Enbrel® 0.4mg/kg) twice a week was introduced on August 2, 1999, parallel with cyclosporine (3.7 mg/kg) and glucocorticoid (Prednisolon® 0.4 mg/kg on alternate days). Subsequently, the patient had several minor upper respiratory tract infections and a varicella zooster infection, but had no joint symptoms or detectable synovitides.

In November 1999 etanercept was discontinued when a red, rough, urticaria-like rash with prurigo appeared on the extensor sides of the elbow skin 1 -2 days after injection. Similar changes were seen on the extensor surfaces of the knees. The size of the urticarial manifestations was of the order of 5 x 4 cm. A more diffuse, less markedly papular rash was observed on the buttocks. A disturbing, if not intolerable, pruritus was felt at the sites of skin manifestation, but not elsewhere. No eye-lid swelling or facial rash was seen. No local treatment was applied. The manifestation disappeared totally, leaving no discoloration suggestive of extravasation within 3 days from the last injection. No eosinophilia was detected during treatment with etanercept. In her case IV immunoglobulins could not be tried, since she had previously developed headaches after such infusions. She has been taking naxopren 125 mg twice daily regularly since her arthritis was diagnosed. She has had no arthritis since November and is being maintained on cyclosporine and alternate-day prednisolone (0.25 mg/kg).

Discussion

Up to now, 26 patients with JIA have been treated with bi-weekly etanercept injections (0.4 mg/kg; treatment duration 3-10 months) in the Rheumatism Foundation Hospital. In most cases the response has been positive: 19 have attained full remission; 2 of these had a relapse after several months, and in 3 other cases (including those described above) the drug had to be withdrawn because of side effects. The third patient had an immediate injection site skin reaction, with exacerbation after subsequent injections and the therapy was abandoned after the third dose. One patient derived no benefit whatsoever from the therapy, while the remaining 6 showed some amelioration in their disease course. Two patients had herpes zooster, for which reason the therapy was withheld until the skin eruption had healed. These overall favorable results are in agreement with those of the Cincinnati group (1, 3).

The two cases described here showed strikingly similar clinical features with progressive urticaria-like rash with prurigo. However, the role of the preceding upper respiratory tract infection is not clear, as the infections could, as previously documented, be connected with etanercept treatment (1, 2). The rash subsided upon discontinuation of the drug, and no eosinophilia was detected during the treatment. Unfortunately no biopsies were taken. Treatment with other drugs was continued in both cases, thus ruling out their possible effect on the rash. In one case the therapy with etanercept could be continued when combined with regular IV immunoglobulin infusions.

JIA patients on etanercept therapy are severely ill and most likely take other drugs as well. In cases with allergic-looking skin manifestations the possibility of etanercept being implicated should be taken into account.

References

1. LOVELL DJ, GIANNINI EJ, WHITMORE JB, SOFFES L, FINCK BK: Safety and efficacy of tumor necrosis factor receptor P75 protein (TNRF:Fc, Enbrel®) in polyarticular course juvenile rheumatoid arthritis. *Arthritis Rheum* 1998; 41 (Suppl): S130.
2. JARVIS B, FAULDS D: Etanercept. A review of its use in rheumatoid arthritis. *Drugs* 1999; 57: 945-66.
3. LOVELL DJ, GIANNINI DJ, LANGE M, BURKE D, FINCK BK: Safety and efficacy of Enbrel® (Etanercept) in the extended treatment of polyarticular course JRA. *Arthritis Rheum* 1999; 42 (Suppl): S117.