Beneficial and Rapid Effect of Infliximab on the Course of Toxic Epidermal Necrolysis

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Sir,

Toxic epidermal necrolysis (TEN) is a life-threatening dermatosis characterized by widespread detachment of the epidermis and mucosal erosions. Depending on the area of skin affected, case fatality rates vary from 20% to 60% (1, 2). The main causes of fatality are secondary infections caused by damage to the epidermis and multi-organ failure (2). Recent reports suggest that tumour necrosis factor alpha (TNF-α), released by activated keratinocytes and macrophages, plays a part in the pathogenesis of this disease (1, 3, 4). This implies that a selective TNF-α blockade could be a new and promising type of treatment. Infliximab is a chimeric monoclonal antibody with human and mouse components that binds specifically to both soluble and membrane-bound TNF-α.

CASE REPORT

A 17-year-old female patient without coexisting risk factors was treated for 10 days with trimethoprim plus sulphamethoxazole for an ear infection and sinusitis. Two days later erythema appeared on her face and on the following day she developed a temperature of 38ºC and general malaise. Initially, small blisters filled with serous fluid were noted on her face and trunk. In a tertiary hospital, TEN was recognized and dexamethasone (4 × 16 mg i.v), intravenous immunoglobulin IgG (IVIG) (0.1 g/kg) for 2 days and antibiotics (ceftriaxone) were given. During this first hospitalization the patient's condition worsened dramatically; huge skin blisters appeared on the surface of the merging erythematosus changes, filled with from a few ml to 1 litre of serous fluid. The changes were observed on approximately 80% of the patient's body, including the face, eyelids, ears, throat, chest, buttocks, labia of pudendum and lower and upper limbs. These changes also affected the conjunctivas, mucous membranes in the mouth and near the urinary and reproductive organs. Due to the exacerbation of the patient's general condition, on the fifth day from the appearance of the first cutaneous eruption the patient was admitted to our department. The skin and mucosal changes were widespread and progressive (Fig. 1a). In follow-up, the respiratory system was affected by hypoxaemia and the digestive system by intense exfoliation of oral mucosa, as was the area of the rectum. It was accompanied by an interim hypertransaminasaemia (the highest serum glutamic oxalacetic transaminase (SGOT) values 126 U/l, serum glutamic pyruvic transaminase (SGPT) 176 U/l on the 7th day from the first symptoms), an increasing level of amylases in serum (300 U/l on the 7th day) and an increasing level of amylases in the urine (1623 U/l on the 9th day). Interim hyponatraemia, hypocalcaemia, hypomagnesaemia and hypoalbuminaemia were also observed, in addition to increasing pancytopaenia with a nadir on the 8th day (white blood cell (WBC) 2900/mm^3, absolute neutrophil count (ANC) 1900/mm^3, platelet count (PLT) 57,000/mm^3). During the first days of the second period of hospitalization the patient continued being given IVIG at a dose of 0.4 g/kg body weight to a total dosage of 1.8 g/kg; over 4 days the doses of steroids were gradually decreased and stopped. Due to further progression of the disease and progressive reduced general condition, a single dose 5 mg/kg of infliximab (Remicade®, Schering-Plough, Brussels, Belgium) was administered. Within 24 h the occurrence of new blisters on the patient's body stopped. On the second day after administration the results of laboratory tests (amylases, leukocytes) started to normalize. Within 5 days areas with proper epidermis were observed on the chest (Fig. 1b) and the general condition gradually improved. On the 12th day the condition of the patient was good, 80% of the damaged skin was covered by new epidermis, leaving post-inflammatory hyperpigmentation. After 19 days of treatment she was discharged from hospital (Fig. 1c). In the 6th week from the beginning of the treatment, the nails of the lower and upper limbs started re-growth.

DISCUSSION

At present there is no "gold standard" for TEN therapy (3). The reasons for this are that the pathogenesis is not entirely clear, and only a small number of patients is

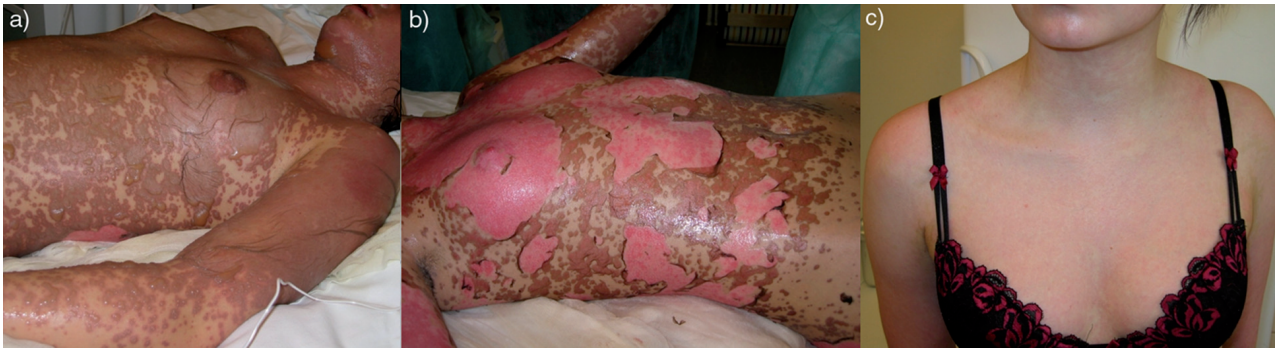

Fig. 1. Toxic epidermal necrolysis (TEN) in a 17-year-old girl. (a) The day before start of treatment with infliximab (face, thorax and perineum). (b) Fourth day after infliximab infusion – re-epithelialization. (c) Nineteenth day after therapy: the skin shows only hyperpigmentation.

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affected and, as a consequence, there are difficulties in planning prospective research (5). In the treatment of TEN many factors have to be taken into consideration e.g. pain, potential serious infections, loss of proteins and liquids, bleeding, hypothermia and multi-organ failure (6). Intravenous application of high doses of glucocorticoids is nowadays recognized as being of very limited use, and such therapy is no longer recommended (2, 3, 5). This factor determined our quick withdrawal of this therapy from our patient. However, recent analysis of 12 cases showed that short dexamethasone puls therapy, given at early stage of the disease, may contribute to a reduced mortality rate without increasing healing time (7). The final value of such medicines as cyclophosphamide, cyclosporine A, N-acetylcysteine, G-CSF remains to be defined (5). Plasmapheresis is recognized as a useful, but costly, method of treatment, especially when combined with immunoglobulin infusion (2). Reports about the effectiveness of IVIG are promising, but their influence on the final result of a treatment seems to be controversial (6).

In the case described here the most likely reason for the occurrence of TEN was the application of trimethoprim plus sulphamethoxazole, since it was the only medicine used by the patient prior to her hospitalization. Besides intense multi-disciplinary support treatment, the patient received IVIG, though no clinical improvement was observed and the illness progressed. This might have been due to the doses of IVIG used in our case being too low. Contemporary treatment suggests that early infusion of high doses of IVIG (1 g/kg/day for 3 days) is likely to be effective.

Eventually, the administration of infliximab resulted in spectacular improvement. Within the first 24 h the occurrence of additional skin changes was repressed and on the fifth day the appearance of the first foci of proper epidermis was observed, which is in line with other medical reports on this issue (1). However, we should remember that the usual spontaneous length of necrolysis is 5–6 days. Thus, the alleged effect of infliximab could have been a reflection of "normal" evolution. However, in our case, just before the infusion of infliximab the patient's condition was worsening, and she had new lesions. Therefore, we believe that the rapid and dramatic improvement is due to the infusion of infliximab.

Until now such treatment used to be implemented only in adults with TEN and in children only in, for example, Leśniowski-Crohn's disease and rheumatoid arthritis (1, 4). Our patient was the youngest (17 years of age) of all reported cases of patients being treated with infliximab and had the largest body surface area affected (80%), compared with other cases where it was 30–35% (1, 3). In our case the respiratory and digestive systems were also affected. Taking into account our own successful experience and the positive results of other reports (1, 3, 8, 9), it seems reasonable to conduct a larger trial of infliximab in TEN.

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