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Letter to the Editor

Rapid subcutaneous desensitization for treatment of hypersensitivity reactions to etanercept in two patients with positive basophil activation test

Dear Editor,

Etanercept is a dimeric human recombinant protein composed by tumour necrosis factor receptor p75 and Fc portion of human IgG1. It irreversibly and competitively binds to membrane and circulating TNF- α , preventing its interaction with membrane receptors on immune effector cells.

Etanercept is considered one of the first-line therapies for various inflammatory and autoimmune diseases including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis.¹ However, the development of local and systemic hypersensitivity reactions to etanercept contraindicates its use in sensitized patients.

Adverse reactions induced by biologics are very diverse, and its true incidence is unknown. In the 2012 review of BIOBADASER (Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases), 16 361 adverse events were registered in a population of 6754 patients treated with monoclonal antibodies, mainly to anti-TNF agents. Among these reactions, 2.788 were considered severe and 215 fatal (1.3% of all reactions). The most frequent causes of adverse events were infectious diseases (31%) and malignant neoplasms (19.5%), whereas immune reactions only represented 0.5%.² Immune reactions to etanercept reported in literature include injection site reactions (ISRs) and immediate systemic hypersensitivity reactions such as pruritus, urticaria, angioedema and anaphylaxis, among others.^{3–5}

In controlled trials in rheumatologic indications, around 37% of patients treated with etanercept developed ISRs³ and in some of them they were even the most common adverse event reported.⁴ Additionally, non-neutralizing antibodies against etanercept have been observed in 18.3% of psoriatic patients treated with the drug, although this finding had no apparent effect on safety or efficacy of treatment.⁵ It is thought that ISRs are due to late hypersensitivity reactions (or T cell-mediated type IV immune reactions), and that they could preclude the subsequent administration of the drug.⁶ Zeltser et al.⁷ demonstrated that the perivascular infiltrate of etanercept ISRs consisted primarily of mature activated cytotoxic T lymphocytes. These reactions take several hours (24–48 h). This differs to an IgE-mediated mast cell and basophil activation (immediate type I) allergic response, which is associated with a wheal-and-flare skin reaction and, potentially, systemic anaphylaxis.

Some desensitization procedures initially designed for IgE-mediated reactions have been applied to non-IgE-mediated ones, with seemingly similar outcomes, but involved mechanisms are unknown. Rapid desensitization is a procedure that makes it possible to continue the administration of monoclonal therapies after development of hypersensitivity reactions in cases in which an adequate alternative does not exist,⁸ and a wide variety of desensitization protocols have been reported.^{8,9} Specifically, desensitization protocols to etanercept have been described, and they are performed to date in 6 steps repeated in 3 days.⁹

We hereby describe a successful desensitization 8-step protocol in one day carried out in 2 patients with psoriatic arthritis presenting adverse reactions to etanercept.

Patients and methods

Patient 1: A 52-years-old woman diagnosed with psoriatic arthritis that three hours after injection presented erythema, pruritus and severe oedema (15–20 cm in diameter) at the site of injection after fifth weekly dose of etanercept (Fig. 1A), which lasted for 12 h.

Patient 2: A 37-years-old woman diagnosed with psoriatic arthritis. Two hours after administration of the second dose of etanercept, she presented with pruritus, erythema and oedema (10 cm in diameter) at the site of injection (Fig. 1C) followed by generalized urticaria without angioedema, that lasted for 4 days and required intravenous treatment with 45.5 mg of dexchlorpheniramine and 40 mg of methylprednisolone.

Due to the failure of previous treatment with methotrexate, hydroxychloroquine and prednisone, both patients were referred to the allergy department to consider the possibilities to successfully perform a desensitization procedure to etanercept, a drug that had good responses in the past in both patients.

Basophil activation tests (BAT) and skin tests with etanercept were performed in both cases. The latter consisted of prick tests using the undiluted drug (25 mg/mL) and of intradermal tests using serial dilutions (1:10 and 1:100). Prick tests were examined at 20 min and intradermal tests at 15 min and 24, 48 and 72 h; a result was considered positive when a wheal 3 mm greater of negative control was obtained.

Results

The results of skin tests with etanercept were negatives in both patients. The same tests were done in five healthy controls and skin

Peer review under responsibility of Japanese Society of Allergy.

<http://dx.doi.org/10.1016/j.alit.2016.09.002>

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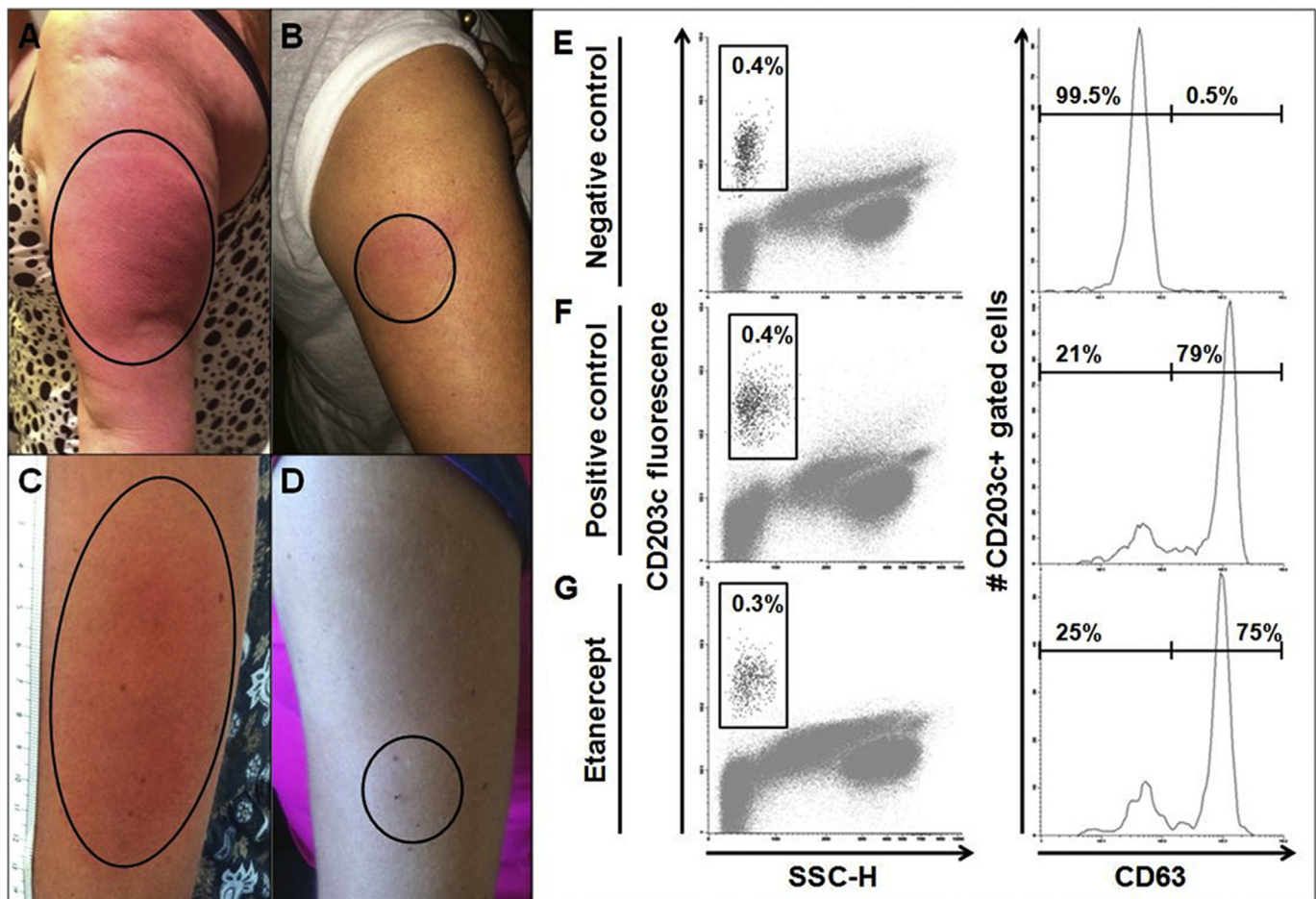


Fig. 1. A, Typical ISR induced by etanercept in patient 1; B, The same patient after etanercept desensitization. C, Typical ISR induced by etanercept in patient 2; D, The same patient after etanercept desensitization. E–G, Results of basophil activation test for patient 1 showing etanercept hypersensitivity. The basophils were identified as SSC^{low}/CD203c^{high}. E, As negative control, background basophil activation with stimulation buffer only (0.5%). F, As positive control, basophil activation with anti-specific IgE antibodies (79%). G, The percentage of activated (CD63+) basophils stimulated by etanercept was 75%.

tests were also negative. By contrast, results of BAT with etanercept were positive in both patients; the percentages of activated basophils by etanercept were 75% in patient 1 (Fig. 1E–G) and 58% in patient 2 (data not shown). The BAT with etanercept results were negative in patients who were treated with etanercept but without hypersensitivity reactions to etanercept. We did not observe a reduction of etanercept induced CD63 expression level in our patients at the end of the etanercept desensitization protocol.

Patients received premedication with dexamethasone (20 mg orally) and dexchlorpheniramine (5 mg intramuscular) 1 h before

the beginning of desensitization protocol. This consisted of subcutaneous administration of 8 doses every 15 min until reaching a cumulative therapeutic dose of 50 mg (Table 1). There were no adverse reactions during desensitization. Fifteen days after desensitization, each patient received a full dose of etanercept divided between the two arms (to avoid high local deposits of the drug) and the full dose in one arm 15 days after. During the last 8 months, patients have been able to continue with etanercept, with minor local erythema resolving within 1–2 h (Fig. 1B and D, respectively).

Conclusions

The recent development of the quantification of basophil activation by flow cytometry represents a new opportunity for the diagnosis of drug allergies. The BAT has proven to be a reliable and valid candidate marker to monitor subcutaneous venom immunotherapy.¹⁰ However, we did not observe a reduction of etanercept induced CD63 expression level in our patients at the end of the etanercept desensitization protocol.

We present a new safe and effective 8-step protocol of rapid subcutaneous desensitization to etanercept in one day, being a valid alternative for patients with adverse hypersensitivity reactions to this drug. Rapid desensitization is a temporary phenomenon that appears to inhibit mast cell activation and mast cell-

Table 1
Subcutaneous desensitization protocol with etanercept.

Dose	Time (min)	Dose administered (mg)	Dilution	Volume administered (mL)
1	0	0.005	1:10000 (0.005 mg/mL)	1
2	15	0.05	1:1000 (0.05 mg/mL)	1
3	15	0.5	1:100 (0.5 mg/mL)	1
4	15	1	1:10 (5 mg/mL)	0.2
5	15	3	1:10 (5 mg/mL)	0.6
6	15	8	1:1 (50 mg/mL)	0.16
7	15	16	1:1 (50 mg/mL)	0.32
8	15	22	1:1 (50 mg/mL)	0.44
Total time = 105 min (1 h 45 min)				

derived mediator release.⁹ Rapid desensitization offers new perspectives to continue the administration of biologic therapies after hypersensitivity reactions in cases in which an appropriate alternative does not exist. This fact represents a major advantage to patients because it shortens the time elapsed to tolerance and to the administration of the optimal treatment for their diseases. However, studies involving a larger number of patients will be needed to evaluate the safety and efficacy of this rapid desensitization approach in patients with ISR to etanercept.

Conflict of interest

The authors have no conflict of interest to declare.

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Received 9 June 2016

Received in revised form 14 September 2016

Accepted 17 September 2016

Available online xxx